DECEMBER 1960
VOL. XXII NO. 6

Circulation

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

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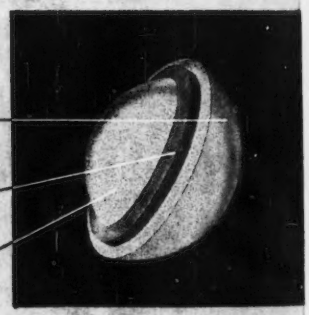

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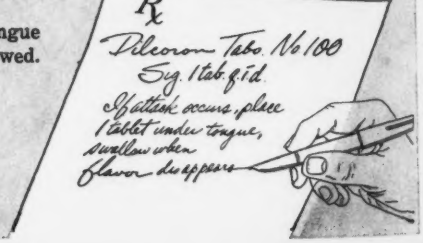

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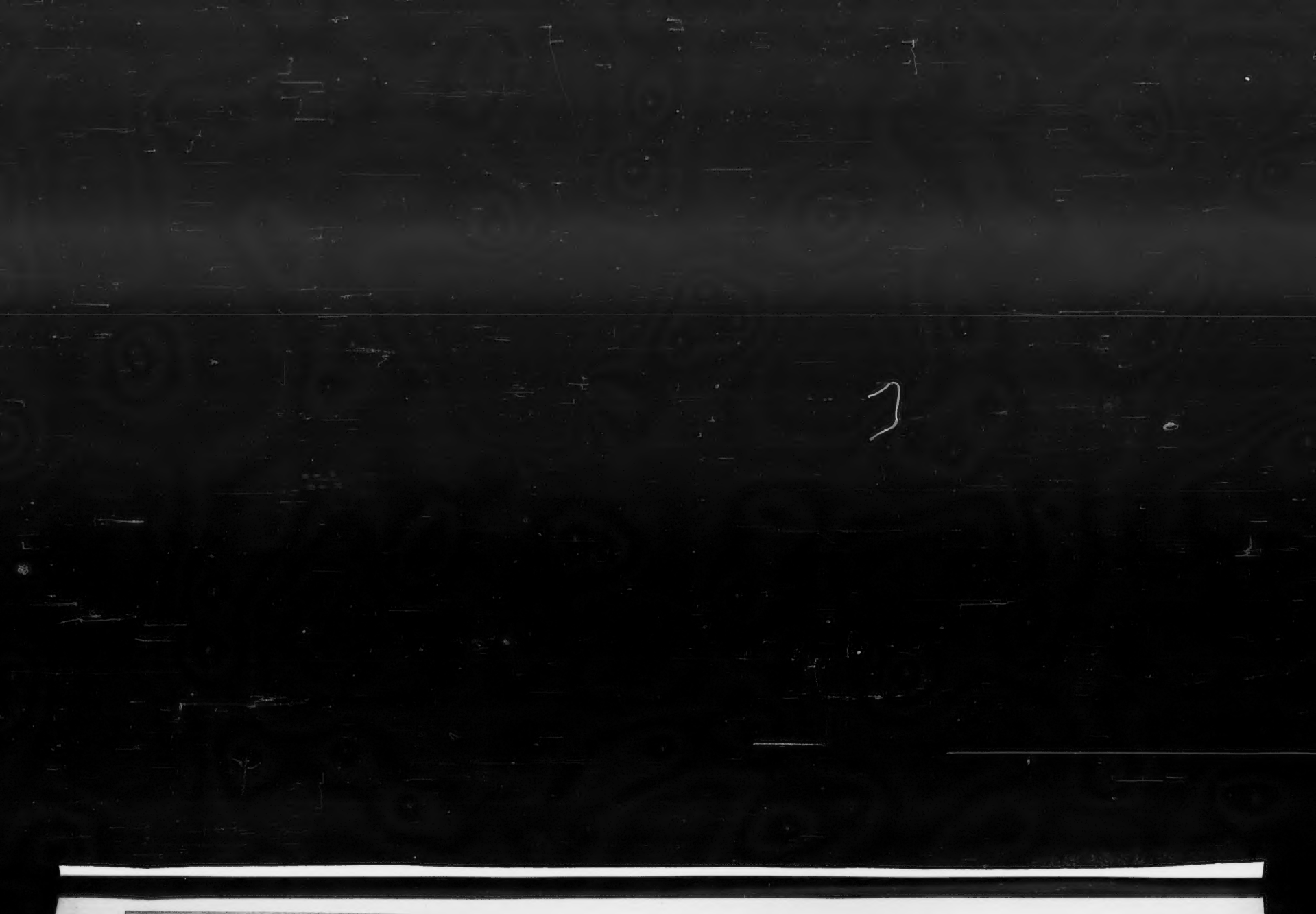

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Editorial

Pulmonary Arterial Hypertension in Congenital Heart Disease

GREAT STRIDES have been made in the surgery of congenital heart disease during the past 20 years. The progress that dates from the first ligation of a patent ductus arteriosus in 1938, and culminates in the successful use of the pump-oxygenator technic in open-heart surgery, has made approximately 85 per cent of the defects in patients over 2 years of age potentially correctible today.

The advent of these technics, and the understandable enthusiasm of cardiac surgeons for them, places a particular responsibility on the cardiologist. Indication for and optimal timing of corrective surgery may be very difficult to determine in the individual case.

In the lesions grouped under the heading of "left-to-right shunts," which includes atrial and ventricular defects as well as patent ductus arteriosus, the question of operative indication is tied closely to the problem of pulmonary hypertension.

When surgery on patent ductus arteriosus was first begun, it became obvious that patients with significant elevation of the pulmonary arterial pressure did not tolerate division of the ductus as well as those without pulmonary arterial hypertension. The same observations were made in regard to correction of atrial defects and more recently in regard to ventricular defects.

These experiences led to closer examination of the problem and resulted in the recognition of at least two kinds of pulmonary hypertension in congenital heart disease. The one, due to an abnormally high pulmonary flow, is commonly referred to as hyperkinetic; the other, associated with nearly normal or even diminished pulmonary flow but high pulmonary vascular resistance, is designated as obstructive pulmonary hypertension. It has been proposed that closure of systemic-pulmonary communications, with principally obstructive pulmonary hypertension, is dangerous and seldom benefits the patient. Contrariwise, if the pulmonary arterial hypertension is predominantly the result of a large pulmonary flow, then correction of the defect is likely to benefit the patient and surgery does not entail prohibitive risk. To put it in another way, septal defects and patent ductus should be closed in order to eliminate a sizable left-to-right shunt; this, in turn, may result in a significant drop in pulmonary arterial pressure due to a reduction of pulmonary blood flow. Conversely, little or no benefit and only high mortality rates may be expected from the closure of defects not allowing an appreciable left-to-right shunt in patients with high resistance (obstructive) pulmonary arterial hypertension.

These concepts having been widely accepted, the next question to answer is whether one should aim at operation early in infancy to avoid "development" of obstructive hypertension. A survey of catheterization data of 500 patients with left-to-right shunts from our clinic indicates that there is no significant

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difference between infancy and childhood with regard to the percentage of patients with significant pulmonary arterial hypertension or pulmonary vascular obstruction except, possibly, in individuals with patent ductus arteriosus. In the latter group there seems to be some increase in the percentage of patients with pulmonary vascular obstruction in children over 3 years as compared to infants. Since most of the older patients with patent ductus arteriosus are not studied by cardiac catheterization, this observation may be related to patient selection. There is no evidence of a significant increase, however, in the percentage of patients with pulmonary arterial hypertension, or pulmonary vascular disease, among the atrial septal defect secundum, atrial septal defect primum group up to 20 years of age, and among the ventricular defects up to 13.

These statistical evaluations of single observations on a large number of patients have been confirmed by repeat catheterization studies on smaller groups of individuals with ventricular defect in our laboratory as well as in other centers in the United States. These studies fail to show any increase in pulmonary arterial mean pressure or calculated resistance through a 5-to-10 year follow-up period, except in a very few cases, in which already elevated resistances became very high in later childhood. Although it is suggested, on the basis of histologic studies, that the nature of pulmonary vascular obstruction may be different at various age periods during infancy and childhood, no clinical confirmation is available at the present time. Finally, serial electrocardiographic studies in 50 children with ventricular defect showed emergence of right ventricular hypertrophy from previously normal or left ventricular hypertrophy tracings in only 2 cases.

Consequently, it seems fair to say that with the possible exception of infants with a patent ductus arteriosus, patients with a left-to-right shunt are unlikely to *develop* progressive pulmonary hypertension or pulmonary vascular obstruction throughout the pediatric age group. It further follows then, that surgical closure of septal defect in early infancy is justifiable only if the patient's symptomatology cannot otherwise be controlled or, as an elective procedure, if the mortality rate in the infant age group may be proved to be as low as it is in older children. Published results indicate that surgery of septal defects is a much safer procedure in children over a few years of age than in infants. Until such a time when surgery can be performed with equal safety in infants and children, there is no justification for elective surgery on septal defects in order to "prevent the development of pulmonary vascular disease."

From these thoughts on pulmonary hypertension and consideration of other factors, it seems reasonable to propose the following time table for operation on left-to-right shunt patients.

1. Patent ductus arteriosus: Excepting patients with small defects not causing significant cardiac enlargement, the patent ductus should be divided as soon as the diagnosis is established. The mortality of surgery in infancy is not significantly higher than during childhood and there is some suggestive evidence that pulmonary vascular changes may develop throughout the pediatric age group.

2. Atrial septal defect, secundum: Optimal age for surgery is between 10 and 20 years. Cardiac bypass is technically easy during this period. After this time pulmonary vascular disease is relatively common. The presence or absence of anomalous pulmonary veins does not influence the timing of operation.

3. Endocardial cushion defect or atrial septal defect, primum: These should optimally be operated upon between 5 and 10 years of age. The serious prognosis of these lesions, principally in terms of congestive failure but also in regard to pulmonary vascular disease, may necessitate surgery at an even earlier time.

4. Ventricular septal defect: Surgery on ventricular septal defects probably ought to be performed before the teens to avoid the possible progression of pulmonary vascular obstruction as well as to avoid an unnecessary

strain on the myocardium. Attempts at complete correction of these defects within the first years of life, in view of the prevailing surgical mortality is probably justifiable only as a last resort at the present time. The exact timing of operation between infancy and adolescence will depend on the condition of the individual patient and the preference of the surgeon. Fear of progression of pulmonary vascular disease should not be a deciding factor in this regard.

ALEXANDER S. NADAS
ABRAHAM M. RUDOLPH
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Aneurism of the Aorta; Singular Pulsation of the Arteries, Necessity of the Employment of the Stethoscope

BY DOMINIC JOHN CORRIGAN, M.D.
Lecturer on the Institutes and Practice of Medicine; one of the Physicians of the Sick-Poor Institution, Dublin.

Suppose an aneurism of the arch of the aorta; the pressure of the fluid on its internal surface will be as the area of the surface. The walls of the sac are not at all strong, in proportion to their extent. The same degree of strength that enables an artery, through its small diameter, to resist a distending force, is far from being sufficient for the sides of a cavity capable of containing a pint. The organic contractility of the arterial trunks, arising from the sac (or immediately by it) pressing the mass of fluid through the sides of the sac, and the mere hydrostatic pressure of the column of blood in the carotid, making, on the sides of the sac, a pressure, increasing, as their area, will cause a yielding in its sides, which does not take place in any other part of the arterial apparatus. Hence the arterial branches, the subclavian, brachial, &c., will, from this disproportion in the resistance, become, in some degree, emptied of their contained blood, by pouring it back on the cavity of the aneurism, after each systole of the heart. If the carotid have the area of an eighth of an inch, and contain half an ounce of blood, it produces a pressure of half an ounce upon every eighth of an inch over the interior of the sac. If the internal surface of the sac present an area one hundred or two hundred times greater than that of the base of the acrotid, the pressure on the sides of the sac will increase in the same proportion.—*The Lancet* 1:586, 1829.

Spontaneous Closure of Ventricular Septal Defects

By J. R. EVANS, M.D., R. D. ROWE, M.B., AND J. D. KEITH, M.D.

SYSTOLIC MURMURS heard during the first year of life in apparently healthy children are commonly noted to have disappeared at a later examination.[1, 2] The exact origin of such murmurs is not known but it has been suggested that some are accounted for by exaggeration of the physiologic pulmonary systolic murmur and a few by late closure of the ductus arteriosus. Of particular interest is a small group of patients in whom a confident clinical diagnosis of ventricular septal defect was made at the initial examination on the basis of the site and quality of the murmur, yet as the child grew the murmur diminished and ultimately disappeared completely. The results of special investigations in a few of the patients support the clinical impression that these murmurs arise from a ventricular septal defect that closes spontaneously.

Method

All patients were seen in the cardiac department of the Hospital for Sick Children, Toronto, during the period 1949 to 1959. They were divided into 3 groups.

In the first group were 37 apparently healthy children in whom a diagnosis of ventricular septal defect had been made at the first examination but in whom disappearance of the murmur was confirmed by subsequent examinations. Thirty-one of the patients were seen during the first year of life. In each case the diagnosis was based on the clinical assessment including electrocardiographic and radiologic examination but in 4 of the patients cardiac catheterization was performed while the murmur was present and in 1 it was repeated after the murmur had disappeared.

The second group consisted of 9 patients with clinical features typical of the preceding group but in whom the murmur had not yet disappeared at the time of writing. In 5, the murmur was recorded on a Sanborn phonocardiogram with a photographic recorder. Cardiac catheterization was done in each case. In 1 patient the catheter passed through the foramen ovale and cineangiocardiography was performed with injections of 5 ml. of 90 per cent Hypaque (sodium diatrizoate) into the left ventricle. In 3 others, sound tracings were made from the pulmonary arteries, right ventricle, and right atrium with an intracardiac phonocatheter and the Sanborn recorder. The tracings were compared with external phonocardiograms taken at the same time in the third and fourth intercostal spaces at the left sternal border.

The third group included 1 patient seen during the first 6 months of life with the clinical picture of a large ventricular septal defect and congestive heart failure. Cardiac catheterization was done when the patient was first seen and repeated at 7 years of age when the clinical signs of heart disease had disappeared. This patient was not included in the first group because of the serious nature of the heart disease with which she presented initially.

Observations

Patients with Murmurs That Disappeared

Clinical Features

A diagnosis of ventricular septal defect based on clinical findings was made in 37 children in whom the murmur ultimately disappeared. None of the patients had cardiac symptoms and all but 2 were referred for assessment of a systolic murmur noted on routine examination. One patient experienced frequent respiratory infections and another had unexplained cyanotic attacks. Three patients weighed 2.5 Kg. or less at birth: 1 was a discordant twin. Transient respiratory distress in the neonatal period was recorded in 1 patient and denied in 30 others; in 6 information was not available.

On examination all the patients appeared healthy without cyanosis, respiratory distress, or signs of congestive heart failure. The systolic murmur was moderately loud, usually grade II (of 4 grades), and was of uniform intensity throughout systole beginning with the first sound and extending to or stopping short of the second heart sound. No midsystolic accentuation was evident. A consistent

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Aided by a grant from the Ontario Heart Foundation.

feature was the superficial blowing quality of the murmur, giving the impression of high-frequency vibrations arising immediately under the diaphragm of the stethoscope. The site of maximum intensity was always in the third and fourth intercostal spaces at the left sternal border. There was no radiation to the axilla or neck vessels. The murmur did not vary with respiration but its duration and intensity decreased markedly in a few patients during the Valsalva maneuver. A faint systolic thrill accompanied the murmur in 6 infants, all of whom were under 6 months of age. In these cases the murmur was usually of grade III intensity. At a second examination under 1 year of age the thrill had disappeared in every instance. The heart sounds, when described, were normal except for 2 infants in whom mild accentuation of pulmonary valve closure was heard. In no instance was an ejection click or diastolic murmur noted. A third heart sound was heard in some patients and a venous hum was present in 2 of the children.

The electrocardiogram never revealed striking abnormalities, and in 24 of the patients it was completely normal. Incomplete right bundle-branch block occurred in 5 patients and in 1 other right ventricular hypertrophy was indicated by an upright T-wave in lead V_1, where the ratio of R/S was greater than 1. Left ventricular hypertrophy was present in 4 patients and evidence of combined left and right ventricular hypertrophy was noted in 3 others: in each instance the abnormal tracing was taken during the first year of life and subsequent electrocardiograms after 1 year of age were normal.

Radiologic examination of the heart and pulmonary vascular markings was normal in all patients over 1 year of age. In 6 infants, age 1 to 7 months, there was some cardiac enlargement with a cardiothoracic ratio ranging from 0.55 to 0.61; in 2, the left atrium was enlarged, and in 4 the hilar shadows were increased. Prominent vascular markings without apparent cardiac enlargement were seen in 2 other patients. All radiologic changes had reverted to normal by 1 year of age.

The arterial oxygen saturation was assessed by ear oximetry in 13 patients at rest and with crying and was found to be over 90 per cent in every case.

At subsequent examinations over the years the systolic murmur tended to decrease in intensity and become shorter. With some murmurs a decrescendo quality about midsystole was recognized. Shortly before the murmur disappeared, it occupied only the first third of systole. The age at which the murmur finally disappeared varied greatly but in the majority of cases it was gone by 2 years of age. In 7 children it persisted beyond 3 years, and in 1 the murmur did not go until the child was between 9 and 10 years of age. After the murmur disappeared no abnormal physical signs could be detected. In 10 patients a soft ejection systolic murmur with low-frequency vibrations was heard in the pulmonary area. The site and quality of this murmur, often heard in normal children, clearly differentiated it from the disappearing type of murmur.

Cardiac Catheterization

Four of the 37 patients in whom the systolic murmur disappeared were submitted to cardiac catheterization while the murmur was still present. The results are shown in table 1. There was evidence of a left-to-right shunt in each case. In 1 patient, D.L., the over-all rise in oxygen saturation was only 2 per cent but 1 sample of 85 per cent in the right ventricle helped to confirm the presence of the shunt. In the other 3, the increase ranged from 7 to 18 per cent, indicating a mild to moderate shunt. The intracardiac pressures were normal in 3 patients, but in D.B., who had the largest shunt, moderate elevation of right ventricular, pulmonary artery, and mean "wedge" pressures was noted.

At 6 months of age patient F.S. had a long systolic murmur and a rise in oxygen saturation of about 10 per cent at right ventricular level. When he was seen at 3 years of age, the murmur was very short and early in systole. The patient was catheterized again 3 months later but at that time the murmur

Table 1

The Results of Cardiac Catheterization in Four Patients with a Clinical Diagnosis of Ventricular Septal Defect in Whom the Systolic Murmur Subsequently Disappeared

Patient (age)	Oxygen saturation (%)						Pressure (mm. Hg)				
	S.V.C.	I.V.C.	R.A.	R.V.	P.A.	Syst. art.	R.A. (mean)	R.V.	P.A.	"Wedge" (mean)	Syst. art.
D. L. (5 wk.)	73	75	73	73 85	75	95	3	25/2	25/10	6	75/3
L. N. (6 mo.)	63	69	59 62	67 69	70 72	90*	0	30/3	30/15	9	—
D. B. (7 mo.)	56	—	57	74	75 75	94	1	55/0	45/15	12	80/3
F. S. (6 mo.)	58	66	55 60	56 71 71	66 67	—	4	30/5	27/10	8	—
(3¼ yr.)†	59	77	63	61	63	—	3	20/5	20/6	—	—

*Measured by ear oximetry.

†Catheterization was repeated and found to be normal after the murmur had gone.

had disappeared completely and could not be demonstrated with the intracardiac phonocatheter. No sign of left-to-right shunt persisted and the right ventricular and pulmonary artery pressures were normal (table 1).

Patients with Probable Disappearing Murmurs

The results of special investigations in 9 additional patients with typical disappearing murmurs are shown in table 2. It should be stressed that in this group the murmur had not disappeared at the time of writing but, from the clinical standpoint, it was considered in each case to be of the type that would eventually disappear. The murmur was not associated with a thrill, and in all patients the electrocardiographic and radiologic findings were within normal limits.

At cardiac catheterization a left-to-right shunt was demonstrated at ventricular level in 5 patients. It is noteworthy that in 1 patient, M.W., the over-all rise in oxygen saturation was negligible but 3 samples taken from the apical region of the right ventricle were 65, 65, and 85 per cent, considerably higher values than in the right atrium or the pulmonary artery. In 4 patients the presence of a ventricular septal defect could not be established by oxygen studies: in patients R.C. and T.G. the rise in oxygen saturation was 2 to 3 per cent at most, and in J.L. and S.B. no increase was noted. No other abnormality was found, however, to explain the systolic murmur in these cases. The right atrial and "wedge" pressure tracings did not suggest tricuspid or mitral incompetence, and no systolic gradient was present between the right ventricle and the pulmonary artery.

Phonocardiographic studies in the 5 patients in whom a left-to-right shunt was demonstrated suggested a correlation between the length and intensity of the systolic murmur and the size of the shunt. The duration of the murmur is represented diagrammatically in table 2. Patients D.M. and R.M. with the largest shunts had grade-II pansystolic murmurs extending from the first sound through to the second sound. On the other hand, in patients J.F. and C.K. the rise in oxygen saturation was less than 5 per cent and the murmur was softer and shorter, terminating in early or midsystole. A soft, short, early systolic murmur with decrescendo quality was present in patient M.W., in whom no increase in pulmonary blood flow was detected (fig. 1).

More precise localization of the site of the defect was attempted with special technics in 4 of the 5 patients in whom a left-to-right shunt had been shown with oxygen studies. In patient M.W. a selective cineangiocardiogram from the left ventricle revealed a small jet of contrast medium passing through the lower interventricular septum into the right ventricle (fig. 2). There was no reflux of dye into the left atrium to suggest mitral incom

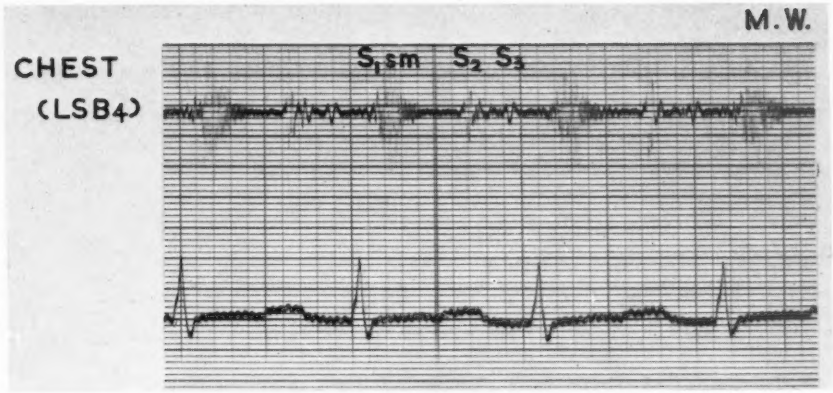

Figure 1

Phonocardiogram of the short, early systolic murmur of patient M.W., in whom a very small defect of the muscular interventricular septum was demonstrated. In this and subsequent tracings the time intervals are 0.04 sec. per small division; S_1, S_2, and S_3 indicate first, second, and third heart sounds respectively; SM indicates systolic murmur.

petence. In 3 other patients, intracardiac sound tracings demonstrated that the murmur was confined to the right ventricular cavity and was not recorded in the right atrium or pulmonary artery. The pansystolic murmur of patient D.M., who had the largest shunt, was well heard throughout the body of the right ventricle (fig. 3). In the other 2 patients with small shunts the murmur was best heard with the tip of the phonocatheter in the apical region of the right ventricle. The murmur of J.F., which occupied the first half of systole, was loudest at the apex of the right ventricle, faint in the body of the right ventricle, and not detected in the outflow tract or tricuspid valve region (fig. 4). A short early systolic murmur was recorded in patient C.K. in the apical region and was not detected elsewhere in the right ventricle (fig. 5). The intracardiac sound tracings of all 3 patients showed murmurs of similar quality and timing to those recorded at the lower left sternal border with external phonocardiography (figs. 3, 4, and 5).

Patient with Large Ventricular Septal Defect

The patient presented at 5 months of age with the signs of a large ventricular septal defect in congestive cardiac failure. The systolic murmur was harsh and of grade-III intensity; it was loudest in the fourth left interspace near the sternum, where a soft thrill was palpable. The electrocardiogram showed evidence of both left and right ventricular hypertrophy. On radiologic examination the heart was moderately enlarged with a prominent left atrium and dense pulsatile hilar shadows. With digitalis therapy the rapid respirations, jugular venous engorgement, and hepatic enlargement all disappeared. Cardiac catheterization at 6 months of age showed a marked rise in oxygen saturation at ventricular level with moderate elevation of right ventricular pressure (table 3.) The pulmonary artery was not entered. At this time, there was no diastolic murmur to suggest patent ductus arteriosus or pulmonary incompetence.

Over the next 2 years the signs of left-to-right shunt gradually diminished. The electrocardiogram and chest x-ray returned to normal. Digitalis was stopped, and the patient remained without symptoms. When the patient was 7 years old no abnormality could be detected on examination, except for a very soft short systolic murmur along the left sternal border. Catheterization was repeated and showed normal intracardiac pressures with no significant left-to-right shunt (table 3).

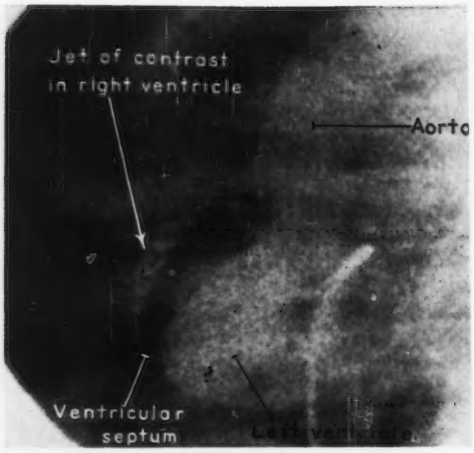

Figure 2

Selective angiocardiogram from the left ventricle (lateral view) in patient M.W., showing small jet of contrast medium in body of right ventricle. Cine-films demonstrated that this jet originated near the apex of the right ventricle.

Discussion

The 37 children with a systolic murmur that diminished and finally disappeared presented characteristic features that should permit recognition of this type of disappearing murmur. The children were healthy without symptoms of heart disease. As a rule the only abnormal sign was the systolic murmur. The electrocardiogram and chest x-ray showed mild changes in a few cases but in the majority they were completely normal. The distinctive feature of the systolic murmur was its superficial blowing quality, suggesting high-frequency vibrations. It was of uniform intensity throughout systole beginning with the first heart sound and usually stopping just before the second sound. The site of maximum intensity was the left sternal border in the third and fourth intercostal spaces with no radiation to the neck or axilla. In no child over 1 year was the murmur accompanied by

Table 2

The Results of Cardiac Catheterization in Nine Patients with the Typical Systolic Murmur of a Ventricular Septal Defect that will Disappear Spontaneously

Patient (age)	Systolic murmur Length S_1	S_2	Grade (1-4)	Oxygen Saturation (%) S.V.C.	I.V.C.	R.A.	R.V.	P.A.	Pressure (mm. Hg) R.A. (mean)	R.V.	P.A.	"Wedge" (mean)
D. M. (2 yr.)			2	58	68	56	67	70 71	1	30/5	25/10	11
R. M. (1 mo.)			2	60	52	62 64	70 71	71 68	0	35/-2	30/8	4
J. F. (4 yr.)			1	44 45	57	46 51 51	54 53 54	55 55	5	18/5	17/7	7
C. K. (6 yr.)			1	59	66	58	57 56 58 64*	63 62 62	2	17/4	17/9	10
M. W. (3 yr.)			1	54	72	54 58	55 65* 65* 85*	54 57 58	1	15/1	13/7	5
R. C. (9 yr.)	short		1	79	87	80 80	82 84 84	83	7	25/10	25/10	4
T. G. (5 yr.)	short		1	70	—	72	74	74	3	17/0	13/3	4
J. L. (14 yr.)	short		1	81	—	83	82 84	84	9	27/7	25/5	8
S. B. (7 yr.)	short		1	77	83	79	78	79	5	25/0	25/10	6

*Sample drawn from apex of right ventricle.

The duration and intensity of the murmur may be compared with the size of the shunt. In 5 patients, the murmur is represented diagrammatically as recorded at the lower left sternal border with the phonocardiogram.

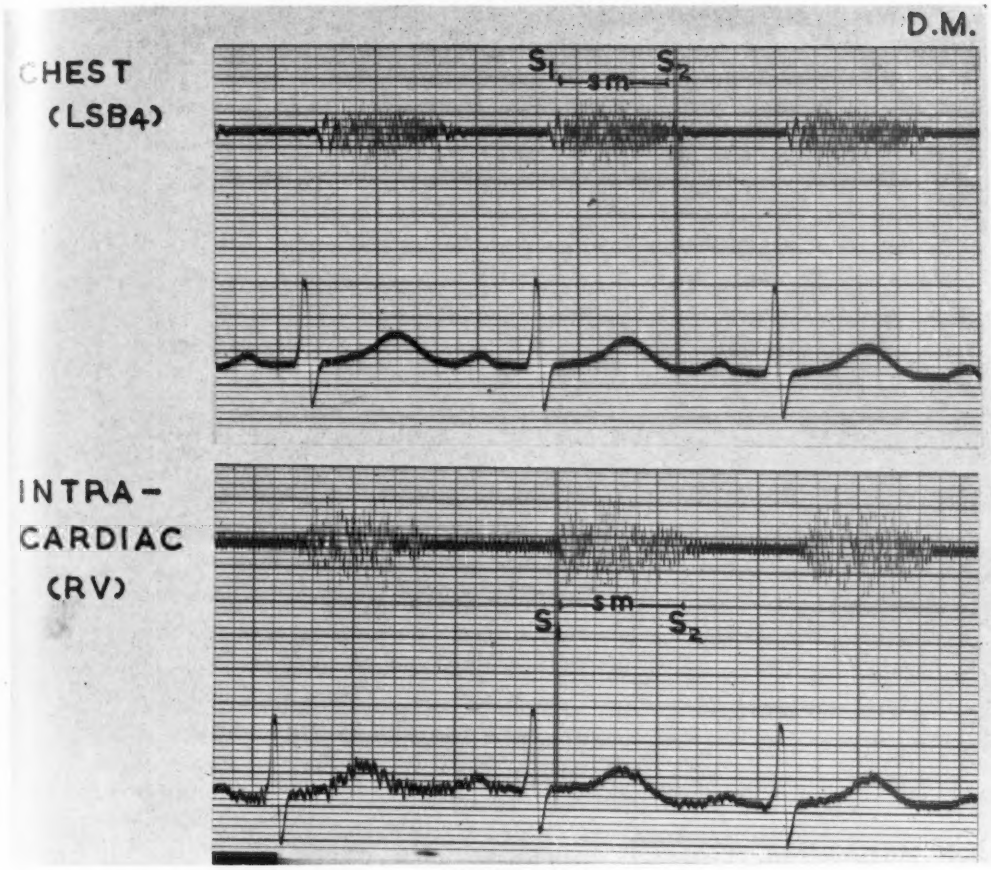

Figure 3

Phonocardiograms of patient D.M. with a moderate left-to-right shunt showing the pansystolic murmur. Lower tracing: *Murmur recorded with intracardiac phonocatheter in right ventricle only.* Upper tracing: *Murmur recorded externally in fourth interspace at left sternal border.*

a thrill. A thrill, however, was noted in 6 infants but in these cases the murmur was louder, pansystolic in length, and electrocardiographic and radiologic evidence of heart disease was present. In each case the abnormal findings including the thrill were gone by the end of the first year and all that remained was the superficial high frequency systolic murmur.

As the children grew older, the systolic murmur became softer and shorter. In some a decrescendo quality was recognized and the murmur terminated about midsystole. The ultimate time of disappearance of the murmur varied greatly. Most were gone by the end of the second year but in one fifth of the present series the murmur persisted beyond 3 years, and in 1 patient it did not disappear until 10 years of age. It is not yet known whether similar murmurs heard in older patients will disappear during adult life.

When the patients were first seen several possibilities were offered to explain the origin of the "disappearing systolic murmur." The site of maximum intensity and the timing of the murmur made ventricular septal defect

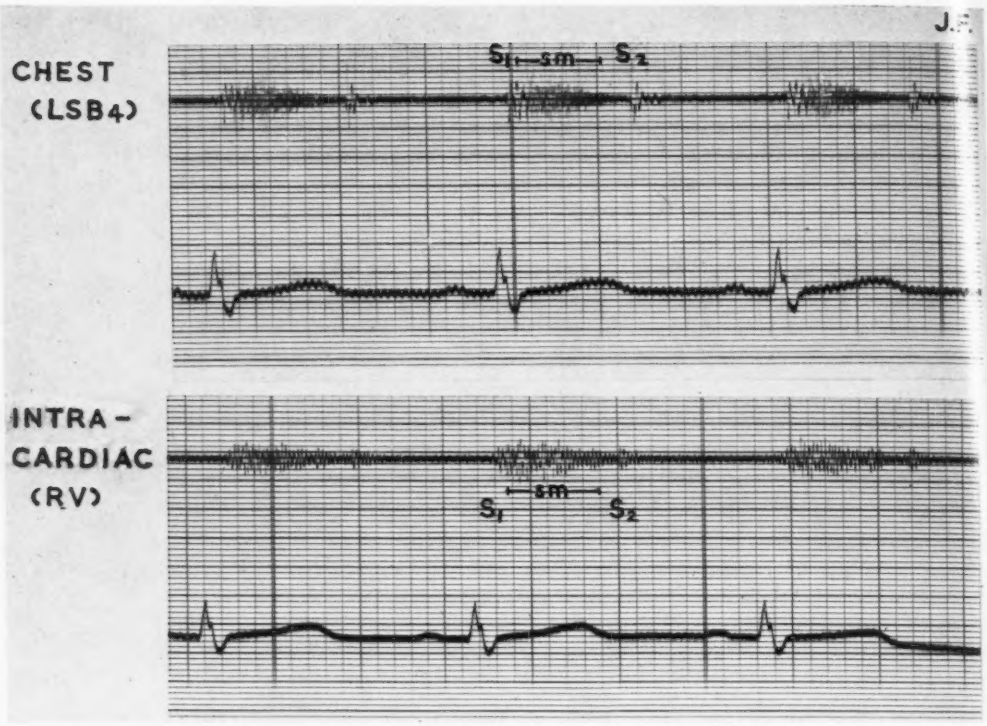

Figure 4

Phonocardiograms of patient J.F. with small left-to-right shunt showing the systolic murmur in the first half of systole. Lower tracing: *Murmur recorded best with intracardiac phonocatheter at apex of right ventricular cavity.* Upper tracing: *Murmur recorded externally in fourth interspace at left sternal border.*

the most probable diagnosis but the superficial blowing quality of the murmur, its termination before the second sound, and the absence of a thrill were all unusual features. Incompetence of the atrioventricular valves was suggested by the blowing quality of the murmur. The site of maximum intensity of the murmur, its lack of radiation to the axilla, and the effect of the Valsalva maneuver militated against mitral incompetence. No inspiratory accentuation of the murmur was recognized nor was there a prominent systolic wave in the jugular venous pulse to suggest tricuspid incompetence. The disappearing murmur lacked the harsh quality, midsystolic accentuation, and palpable thrill found with pulmonary stenosis although it was of similar timing and location to the infundibular type of obstruction. As the disappearing murmur became shorter, its timing resembled the systolic murmur that may arise normally in the pulmonary artery. The latter murmur, however, has a distinctive coarse vibratory quality and is loudest at the upper left sternal border. Originally a broad differential diagnosis was considered in patients who showed the disappearing murmur but in recent years the murmur has been specifically identified without difficulty at the first examination in most cases.

The pathogenesis of the disappearing murmur was clarified by special investigation. A total of 13 patients were catheterized and, of these, 9 were shown to have a ventricular septal defect by oxygen studies, including 4 in whom the systolic murmur subsequently di-

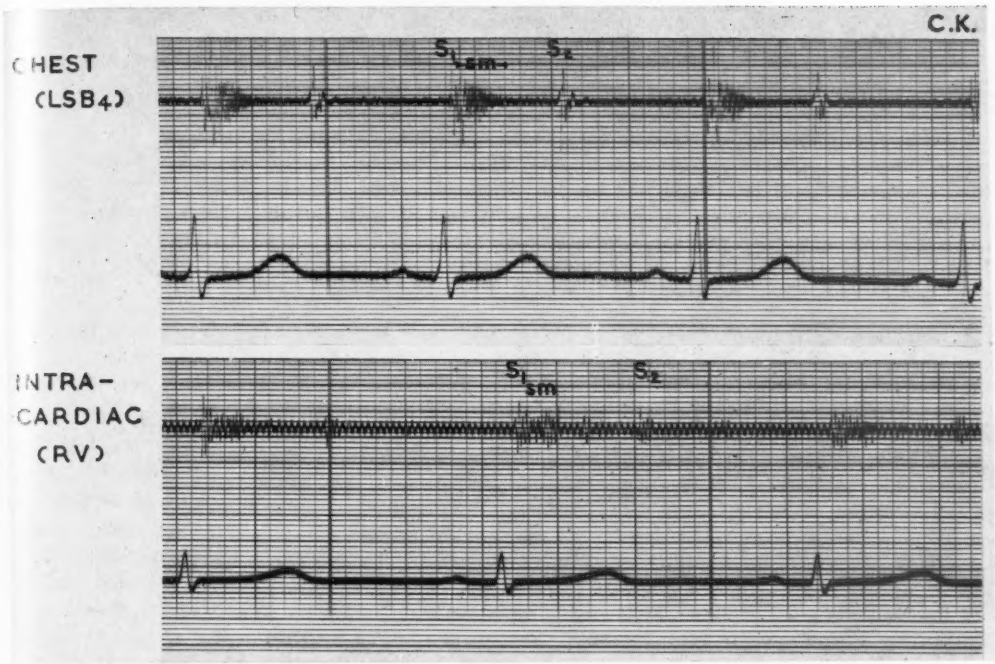

Figure 5

Phonocardiograms of patient C.K. with small left-to-right shunt showing early systolic murmur with decrescendo quality. Lower tracing: *Murmur recorded with intracardiac phonocatheter at apex of right ventricle only.* Upper tracing: *Murmur recorded externally in fourth interspace at left sternal border.*

appeared. The left-to-right shunt was usually small and in a few instances was not apparent, except in samples drawn from the apical region of the right ventricle. In 4 patients no significant rise in oxygen saturation was demonstrated with the routine method of sampling. No evidence of tricuspid incompetence, mitral incompetence, or pulmonary stenosis was found in the pressure tracings of any of the patients. Sound tracings from the right side of the heart in 3 patients with small to moderate left-to-right shunts revealed a systolic murmur confined to the right ventricle that was similar in quality and timing to the murmur recorded externally at the lower left sternal border. The murmur was loudest at the apex of the right ventricle and became softer or imperceptible in the outflow tract and tricuspid valve region. In another patient the interventricular communication was shown by cineangiocardiography to be a small defect in the lower portion of the septum. No significant left-to-right shunt was detected by oxygen studies in this case but samples from the apical region of the right ventricle were consistently higher than those taken elsewhere in the right side of the heart. From these investigations it is apparent that the disappearing systolic murmur arises from a ventricular septal defect although in some patients the left-to-right shunt may be so small that it is not detected on routine sampling. The location of the defect was established in 4 patients and in each case was found to be near the apex of the right ventricle, corresponding to the muscular portion of the interventricular septum.

The natural history of the disappearing murmur appears to follow a characteristic pattern as judged by repeated clinical obser-

Table 3

The Results of Cardiac Catheterization at Six Months and Seven Years of Age in a Patient in Whom the Clinical Signs of a Large Ventricular Septal Defect in Infancy Gradually Disappeared

Age	Oxygen saturation (%)						Pressure (mm. Hg.)				
	S.V.C.	I.V.C.	R.A.	R.V.	P.A.	Systemic artery	R.A. (mean)	R.V.	P.A.	"Wedge" (mean)	Systemic artery
6 mos.	—	31	23	70	—	—	—	60/0	—	—	85/40*
7 yr.	58	—	63 65	63 63	66	93**	4	22/0	19/9	6	100/60*

**Measured by ear oximetry

*Sphygmomanometer.

vations. In infancy the systolic murmur is long and in a few cases the clinical signs may suggest a moderate-sized ventricular septal defect with a pansystolic murmur and thrill, electrocardiographic changes, and radiologic evidence of increased pulmonary blood flow. By the end of the first year all the abnormal signs disappear except the systolic mumur. The murmur becomes progressively shorter and softer and eventually it disappears. A comparison of the character of the murmur in the phonocardiogram and the size of the shunt at cardiac catheterization in 5 patients suggests that the gradual reduction in the intensity and duration of the systolic murmur reflects the decreasing magnitude of the left-to-right shunt. Disappearance of the murmur, therefore, might represent balancing of pressures in the right and left ventricle or a reduction in size of the ventricular septal defect. There is no clinical evidence for the former concept, since the physical, electrocardiographic, and radiologic signs do not reflect the development of right ventricular hypertrophy or pulmonary hypertension. Furthermore, in 1 patient with a proved left-to-right shunt who was catheterized a second time after the murmur had gone, there was no elevation of right ventricular pressure and no residual shunt. It would seem, therefore, that disappearance of the murmur represents closure of the ventricular septal defect. If the defect opened in the inflow region of the right ventricle it could be sealed off by adherence of the septal leaflet and chordae of the tricuspid valve, but the gradual sequence of events and the probable location of the defect in the muscular portion of the septum make this unlikely. Alternatively, the defect could be progressively narrowed by hypertrophy of the muscle of the interventricular septum. This, in our opinion, is the probable mechanism of closure. In the newly born infant the septum is very thin between the trabeculae, particularly in the region near the apex of the heart. With growth of the heart and hypertrophy of its musculature the septum is gradually thickened, and small interventricular communications might be expected to be narrowed and ultimately obliterated. In support of such a hypothesis are the observations of Edwards[3] that defects of the muscular septum in infants are ovoid in shape, whereas in adults they are small and linear with the upper and lower margins almost in apposition. In one 65-year-old man the margins of a small defect in the muscular septum appeared to have fused.[4]

Spontaneous closure of a ventricular septal defect is not a new concept. This phenomenon was suspected on clinical grounds by several physicians but in no instance was the diagnosis proved. The first and best documented case was that described by French in 1918.[5]

Some years ago I saw a small boy, 14 months old, and on examination of the heart there was a loud systolic bruit, with its maximum intensity over the fourth intercostal space, close to the sternum, but audible over the whole precordial region, and indeed over most of the chest, both back and front. It was accompanied by a thrill near the sternum, and those of you who have seen congenital heart cases in the wards will realize the kind of case it was when I say that

the diagnosis made by myself and others was congenital perforation of the interventricular septum. The father of the boy was an officer in the Navy, and this was his only child. He had always made up his mind that any boy of his should follow him in the service, and it was a tremendous blow to him to find that the child had a bruit which was certain to cause his rejection at the medical examination . . .

I saw the boy again when he was two years old, and the bruit was about the same as before, very loud and universal. I saw him again when he was five, *and there was then absolutely no bruit at all!* I saw him again at the age of ten; and he was still without a bruit and had no objective evidence of any heart lesion. The father's keen desire that the boy should follow him in the service has since been gratified and the case has taught me that the bruit of a congenital malformation of the heart may disappear as a child grows up.

French considered that the murmur disappeared because the defect did not enlarge in proportion to the growth of the heart. Other probable examples of disappearance of a ventricular septal defect are cited by Stamm,[6] Weber,[7] Still,[8] Perry,[9] and Muir.[10] Weber[7] postulated that contraction of the fibrous tissue around an aperture in the interventricular septum might diminish the size of the defect or close it off completely.

The paucity of case reports in the literature would suggest that spontaneous closure of a ventricular septal defect is rare. The present series of 37 patients was culled from over 120 patients seen in a 10-year period in whom the disappearing type of murmur was present. The remainder of the clinical cases were not included, since the murmur was not followed to complete disappearance. Probably other examples of this condition in older children were dismissed as functional murmurs, since no abnormality was detected apart from the murmur. With our current awareness of the syndrome an increasing number of cases have come to our attention. During the last 5 years in the practice of one of us (R.D.R.) 217 cases of ventricular septal defect have been seen, and 54 of these would seem to be the disappearing type of defect. Furthermore, in a recent survey of 80 "normal" newly born, term infants the typical superficial blowing systolic murmur, beginning with the first sound and stopping before the second sound, was heard in 3.[11] If the proposed concept of the pathogenesis and disappearance of the murmur is correct these data suggest that small defects in the muscular ventricular septum that close with growth of the heart are relatively common.

Spontaneous closure is not confined to small defects. The patient who presented with congestive failure had the clinical signs of a major left-to-right shunt in keeping with a large ventricular septal defect. The exact site of the defect was not demonstrated. The mechanism of closure is uncertain but the clinical and hemodynamic evidence of a gradual reduction in the left-to-right shunt over several years is in keeping with the concept that muscular hypertrophy of the septum, perhaps augmented by the abnormal cardiac workload, narrows the septal defect and eventually obliterates it.

Recognition of the fact that small defects of the muscular ventricular septum will close without treatment is of practical importance. These lesions are not uncommon; they can be identified by clinical assessment with reasonable certainty; and, the prognosis is uniformly good. Spontaneous closure of large ventricular septal defects, however, must be rare and unfortunately the clinical signs are not sufficiently distinctive to permit prediction of a favorable outcome.

Summary

A group of 37 children is described in whom a systolic murmur heard early in life gradually diminished and eventually disappeared. When the patients were first seen, the clinical findings suggested a small ventricular septal defect but no thrill was present and the systolic murmur had a superficial blowing quality with high-frequency vibrations and tended to stop before the second heart sound. Cardiac catheterization demonstrated a small left-to-right shunt at ventricular level in 4 of the patients while the murmur was present; in 1 this was repeated after the murmur had gone and no abnormality could be demonstrated.

Cardiac catheterization in other patients with typical disappearing systolic murmurs showed a left-to-right shunt in some but in others this was too small to be detected by routine oxygen studies. A rough correlation was established between the length and intensity of the murmur and the size of the shunt. With angiocardiography and intracardiac phonocardiography the exact site of the ventricular septal defect was localized to the muscular portion of the septum in 4 of the patients.

In 1 patient who presented with congestive heart failure, clinical and hemodynamic findings of a large ventricular septal defect diminished over several years and finally disappeared.

Children with the specific type of systolic murmur described may be recognized as having a small defect in the muscular ventricular septum. The defect is thought to be gradually reduced in size and ultimately closed by hypertrophy of septal muscle. Spontaneous closure appears to be not uncommon with small ventricular septal defects and may rarely occur with lesions large enough to present with congestive heart failure.

Summario in Interlingua

Es describite un gruppo de 37 juveniles in qui un murmure systolic, audite tosto in le curso de lor vitas, se reduceva gradualmente e dispareva in le curso del tempore. Quando le patientes esseva primo vidite, le constatationes clinic suggereva un micre defecto ventriculo-septal, sed nulle fremito esseva presente, e le murmure systolic habeva un qualitate de sufflation superficial con vitrationes alti-frequential e tendeva a arrestar se ante le secunde sono cardiac. Catheterismo cardiac demonstrava un micre shunting sinistro-dextere al nivello ventricular in 4 del patientes durante le tempore quando le murmure esseva presente. In un, le catheterismo esseva repetite post le disparition del murmure, e nulle anormalitate poteva esser demonstrate.

In altere casos typic de disparente murmures systolic, le catheterismo cardiac monstrava, in plures, un shunting sinistro-dextere, sed frequentemente isto esseva troppo micre pro esser detegite per routinari studios de oxygeno. Un crude correlation esseva establite inter le longor e le intensitate del murmure e le magnitude del shunting. Per medio de angiocardiographia e phonocardiographia intracardiac le exacte sito del defecto ventriculo-septal esseva fixate in le portion muscular del septo in 4 del patientes.

In 1 caso, presentate con congestive disfallimento cardiac, le constatation clinic e hemodynamic de un grande defecto ventriculo-septal se attenuava in le curso de plure annos e finalmente dispareva.

Juveniles con le typo specific del hic-describite murmure systolic pote esser recognoscite como sufficiente de un micre defecto in le portion muscular del septo. Es opinate que le defecto reducite gradualmente e claudite ultimemente per hypertrophia del musculo septal. Il pare que le clausion spontanee de micre defectos ventriculo-septal non es incommun. In rar casos, clausion spontanee pote occurrer quando le lesion es satis marcate pro presentar le symptomas de congestive disfallimento cardiac.

References

1. TAYLOR, W. C.: The incidence and significance of systolic cardiac murmurs in infants. Arch. Dis. Childhood 28: 52, 1953.
2. KEITH, J. D., ROWE, R. D., AND VLAD, P.: Heart Disease in Infancy and Childhood. New York, The Macmillan Company, 1958, p. 15.
3. EDWARDS, J. E.: Congenital malformations of the heart and great vessels. *In* Pathology of the Heart. Edited by S. E. Gould. Springfield, Ill., Charles C Thomas, Publisher, 1953, p. 288.
4. —, DRY, T. J., PARKER, R. L., BURCHELL, H. B., WOOD, E. H., AND BULBANIAN, A. H.: An Atlas of Congenital Anomalies of the Heart and Great Vessels. Springfield, Ill., Charles C Thomas, Publisher, 1953, p. 67.
5. FRENCH, H.: The possibility of a loud congenital heart murmur disappearing when a child grows up. Guy's Hosp. Gazette, N. S., 32: 87, 1918.
6. STAMM, L.: Letter to the Editor. Guy's Hosp. Gazette, N. S., 32: 146, 1918.
7. WEBER, F. P.: Can the clinical manifestations of congenital heart disease disappear with the general growth and development of the patient? Brit. J. Child. Dis. 15: 113, 1918.
8. STILL, G. F.: Common Disorders and Diseases of Childhood. Ed. 4. London, Oxford University Press, 1924, p. 585.
9. PERRY, C. B.: Discussion on the course and management of congenital heart disease. Proc. Roy. Soc. Med. 30: 693, 1937.
10. MUIR, D. C.: Discussion on the course and management of congenital heart disease. Proc. Roy. Soc. Med. 30: 698, 1937.
11. BRAUDO, M., AND ROWE, R. D.: The heart sounds in the newly born infant. A.M.A.J. Dis. Child. 98: 568, 1959.

Raynaud's Disease and Primary Pulmonary Hypertension

By GUILLERMO C. CELORIA, M.D., GILBERT H. FRIEDELL, M.D., AND SHELDON C. SOMMERS, M.D.

PARTICULARLY since the advent of cardiac catheterization, primary pulmonary hypertension has been of increasing interest to clinicians and pathologists alike. To some it represents a pulmonary vasospastic disease, presumably of neurohumoral type, analogous to systemic essential hypertension. The occasional association of primary pulmonary hypertension with Raynaud's disease is thought to support this theory.

Seven case reports are available in which Raynaud's disease was associated with what was considered to be primary pulmonary hypertension.[1-4] The detailed findings in the case of Taft and Mallory[1] and that of Wade and Ball[2] are of particular interest because of the scarcity of pathologic investigations in cases of Raynaud's disease with or without pulmonary hypertension.

Pulmonary hypertension was confirmed by cardiac catheterization in 3 of the 7 cases, but without autopsy confirmation. One of these 3 catheterized patients (case 2 of Smith and Kroop[3]) has since died, and an autopsy was performed.

Report of Case

N. C., (A58-159). A 41-year-old white married telephone operator was in generally good health until 1951, when she noticed numbness, tingling, and blanching of all fingers up to the palm when exposed to the cold. During the previous several years she had had a cholecystectomy, a breast biopsy, and a total hysterectomy, but no history of Raynaud's phenomenon. Her symptoms gradually progressed so that constant warmth was necessary to prevent pain. Atrophic changes of the fingertips became evident later. In 1953 bilateral thoracic sympathectomies resulted in disappearance of symptoms except for continued blanching of her fingers on exposure to cold. Six months later, during the winter, she developed Raynaud's phenomenon in her toes and subsequently bilateral lumbar sympathectomies were performed in 1954 with good results.

Shortly after the final sympathectomy she began to experience episodes of dyspnea, weakness, and dizziness. These occurred only while she was standing, especially after exertion. She had numbness and tingling of the body during some of these episodes and fainted on several occasions. Blurring of vision was noted at times and scotomata were seen with some of the attacks.

The exertional dyspnea became progressively more severe and in April 1956 she was first admitted to this hospital. The essential clinical feature included (1) a loud and "split" pulmonic second sound, (2) a blood pressure of 135/100 mm. Hg with no appreciable positional change, (3) an enlarged right ventricle and pulmonary artery with normal-size left ventricle and left atrium seen on the roentgenogram, (4) electrocardiographic evidence of right ventricular hypertrophy, and (5) reproduction of some of her symptoms by hyperventilation. Three months later, ankle edema was present. Studies of pulmonary function at this time were indicative of primary pulmonary hypertension.

She was rehospitalized for treatment and further study in October 1956. At that time both right and left ventricular failure were found. Over the upper part of the body there were numerous telangiectases which blanched on pressure. Cardiac catheterization confirmed the diagnosis of marked pulmonary hypertension with advanced right heart failure.

The cardiac catheterization data included cardiac output, 3.8 L. per minute; cardiac index, 2.08 L. per minute per M.^{2}; and arteriovenous oxygen diffusion, 7.2 vol. per cent. Oxygen saturations of the pulmonary artery, 52.3 per cent; right ventricle, 53.9 per cent (paired sample); right ventricle, 47.3 per cent; right atrium, 45.6 per cent (paired sample); superior vena cava, 40.4 per cent; and brachial artery, 93.3 per cent. Pressures recorded in mm. Hg were right atrium 20; right ventricle 105/20; pulmonary artery, 105/40; pulmonary "capillary" 10; and systemic blood pressure, 130/80.

These changes were interpreted by the catheterization team as showing advanced right-sided heart failure from marked pulmonary hypertension. Elevated pulmonary artery pressure and normal pulmonary "capillary" pressure were considered to indicate narrowing of pulmonary arterioles, rather than an element of left-sided heart failure. A detailed analysis of these findings will be reported elsewhere by Chobanian et al.[5]

From the Department of Pathology, Massachusetts Memorial Hospitals, Boston, Mass.

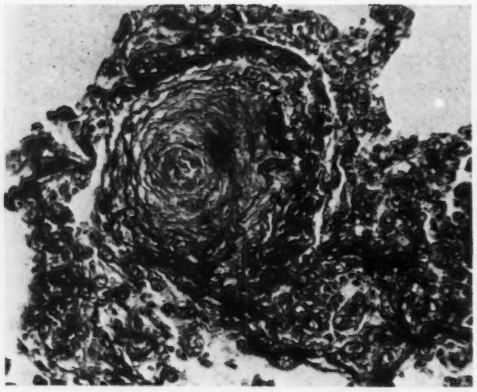

Figure 1

A small muscular artery is seen with extreme narrowing of the lumen, cellular intimal proliferation, and fibrosis. The inner elastic lamina is frayed and in some areas is disrupted. Verhoeff-van Gieson.

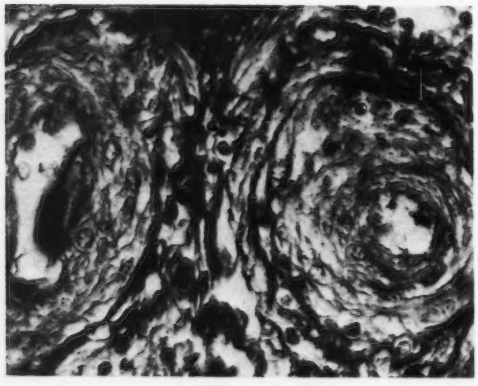

Figure 2

High-power view of small muscular artery on the right and its arteriolar branch on the left shows cellular intimal proliferation in both vessels with narrowing of their lumina. Verhoeff-van Gieson.

Skin and muscle biopsies were reported to show no evidence of scleroderma or other collagen disease. No clinical or radiologic evidence of scleroderma developed later in her course. She was digitalized, given mercurial diuretics, and discharged with the clinical diagnoses of primary pulmonary hypertension and Raynaud's disease.

The patient was subsequently hospitalized on 3 occasions for treatment of cardiac failure. During the last of these, in December 1958, she died after a prolonged period of hypotension. An autopsy was performed 6 hours after death.

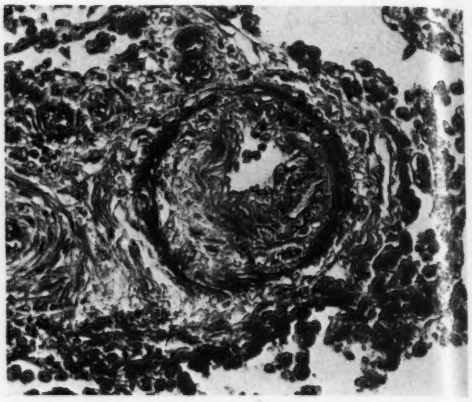

Figure 3

Edema of the wall is seen in this small muscular artery in addition to intimal cellular proliferation and eccentric fibrosis. Masson trichrome.

On gross examination there was cyanosis of the face and of the fingertips. Over the face and chest multiple small dark red-blue areas resembling telangiectases were seen. The skin on all fingers was smooth and shiny, and the fingernails on both hands were short and rough. There was slight peripheral edema.

In the right pleural cavity 300 ml. of yellow-pink watery fluid were found, and the lung appeared collapsed. A few fibrous adhesions were also noted between the lower lobe and the posterior parietal pleura. The left pleural cavity was obliterated by dense fibrous adhesions that somewhat constricted the lung.

There were an estimated 400 ml. of thin, straw-colored fluid in the pericardial cavity. The heart weighed 410 Gm. and was enlarged, due primarily to dilatation and some hypertrophy of the right atrium and ventricle. The ventricle measured 0.7 cm. in thickness, compared to normal thickness of 0.4 cm. The pulmonary artery was dilated and showed some atherosclerosis.

The right lung weighed 210 Gm. and the left 190 Gm. They appeared negative, except for a small amount of pink mucoid material in some of the bronchi. There was moderate dilatation of the pulmonary arterial branches and the largest showed thickening of their walls and scattered yellowish intimal plaques.

The other organs appeared negative, except for an apparent telangiectasis of the jejunum.

Microscopic sections of both lungs showed slight septal fibrosis in some regions, dilatation of a few alveoli with rupture of some of the septa, and mild subpleural fibrosis, but no primary parenchymal disease. In the lung, the primary disease proces

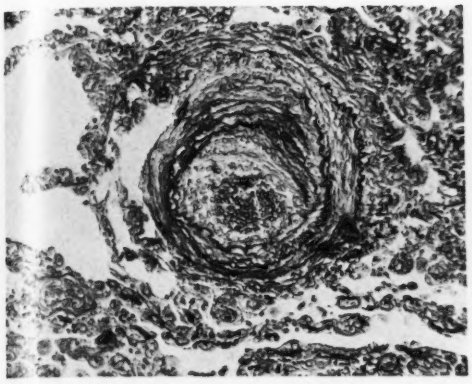

Figure 4

Splitting of the elastic fibers is seen in the upper part of this medium-sized muscular artery, whereas the elastic fibers elsewhere in the inner and outer laminae are rather wrinkled. Cellular intimal proliferation and narrowing of the lumen are also seen. Verhoeff-van Gieson.

Figure 5

Necrotizing arteritis with thrombosis is seen in this medium-sized muscular artery approximately 500 microns in diameter. The wall is infiltrated primarily by neutrophils. There is relatively little proliferative change such as that depicted in smaller muscular arteries. Hematoxylin and eosin.

appeared to be vascular, affecting all branches of the arterial, and to a lesser extent the venous, pulmonary tree.

There was marked atherosclerosis of the larger arteries, with eccentric narrowing of the lumens in the vicinity of subintimal plaques. Oil-red-O stains for fat showed abundant lipid in these plaques and elsewhere in the subintimal tissue. No proliferation of endothelial cells was apparent. There was slight hypertrophy of the muscular media, and elastic fibers were wrinkled and fragmented in some arteries.

The muscular arteries, ranging from 100 to 1,000 microns in diameter, also showed marked change, but of a different type. Below 250 to 300 microns in diameter, the most prominent finding was a marked cellular intimal proliferation with extreme narrowing or occlusion of the lumens (figs. 1 to 3). These hyperplastic cells stained with the Verhoeff-van Gieson stain like smooth muscle.[6] Slight intimal fibrosis was associated in some instances, but the proliferative change predominated.

In the muscular arteries that exceeded 300 microns in diameter, some hyperplasia of endothelial cells was also seen, and moderate edema of many of these cells was noted. The most characteristic intimal change, however, was an eccentric fibrosis of slight to moderate degree (fig. 4).

The media of muscular arteries of all sizes was generally thickened, primarily by an increase in smooth muscle but to some extent by fibrosis. The elastic laminae of medium and small arteries was often wrinkled, thickened, and occasionally fragmented. Edema of the adventitia was evident in most of the muscular arteries of small and medium size.

Acute arteritis was noted in several muscular arteries that ranged from 250 to 500 microns in diameter. These arterial walls showed focal necrosis with neutrophils infiltrating all layers of the wall and the adjacent connective tissue. In some of these vessels thrombi were present, a few of which showed early peripheral organization (fig. 5). A thrombus, possibly of embolic origin, was also noted in one section in a small muscular artery of about 100 microns in diameter, but here there was no apparent arteritis.

In the arterioles the marked intimal cellular proliferation (fig. 6) was also present and the arteriolar lumens were either markedly narrowed or occluded. In some arterioles, particularly those near the parent arteries, smooth muscle persisted in the media while in others the wall contained an increased amount of relatively acellular tissue that stained like fibrous tissue with the Verhoeff-van Gieson stain.

Elsewhere dilated arterioles with thinned walls were noted.[6] Small veins showed moderate to marked subintimal acellular fibrous thickening, but in contrast to arterioles had no endothelial proliferation (fig. 7). Larger veins also had fibrous thickening of their walls and in addition some atherosclerotic changes.

Slight to moderate hyaline coronary arteriolosclerosis and slight interstitial myocardial edema and fibrosis were present. In the spleen, pancreas, and liver there was slight to moderate hyaline thickening of arterioles with narrowing of their

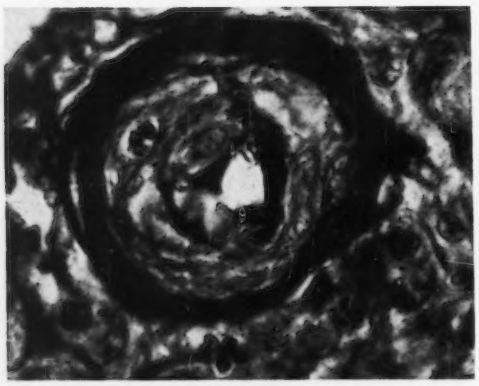

Figure 6

Marked narrowing of small arteriolar lumen by cellular proliferation is seen in this high-power photomicrograph. Verhoeff-van Gieson.

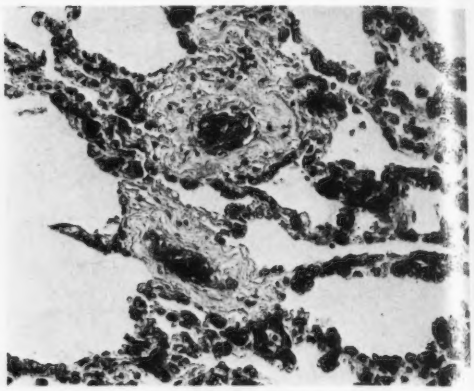

Figure 7

Two small veins with cellular fibrosis of their walls are seen in the center of the field. Marked congestion of alveolar septa is also noted. Masson trichrome.

lumens. In larger arterioles and small muscular arteries there were, in addition, slight hyperplasia of endothelial cells and of medial smooth muscle cells and fraying of adventitial collagen.

Only minimal intimal proliferation and hyaline arteriolosclerosis existed in the kidneys and other organs, except for the skin. Here there was moderate hyaline arteriolar thickening as well as both cellular endothelial hyperplasia and medial hypertrophy of small muscular arteries. Sections could not be obtained from digital vessels.

Discussion

Smith and Kroop[3] in their cases 1 and 3, noted marked pulmonary arteriolar sclerosis. From their photomicrographs there would also appear to have been extensive involvement of small muscular arteries. The subintimal thickenings of the arterial and arteriolar walls appeared to be relatively acellular in character. Taft and Mallory[1] also placed the lesion primarily in the arterioles and drew a parallel between the changes in these vessels and those in "rapidly progressive nephrosclerosis." The thickened arterioles were relatively acellular, and no areas of necrosis were noted.

In their autopsied case, Wade and Ball[2] found the major change to be in the smaller muscular arteries, ranging from 80 to 250 microns in diameter. The lumens of these vessels were reduced by a concentric intimal fibrosis or fibroelastosis characteristically unaccompanied by inflammatory infiltration or degeneration of the media or adventitia. Rare recent but no remote thrombi were noted. An atrial septal defect 2 by 1.5 cm. in greatest dimensions was present in this case and although it was considered by the authors merely as an incidental finding, it could have altered pulmonary dynamics enough to account for the morphologic findings. Similar vascular changes were noted in the digital arteries, pancreas, and kidneys, whereas a focal fibrinoid arteritis was noted in the adrenal glands and a mild cellular arteritis was seen in the liver. Some of the prominent arterial lesions in their case were thought to resemble the changes in scleroderma, whereas other lesions simulated polyarteritis.

The main pulmonary lesion in the present case was vascular also, involving chiefly the small muscular arteries and arterioles. In contrast to the previously reported cases, however, these vessels were occluded by the proliferation of endothelial cells, a change not observed elsewhere in the body. In previous cases the thickening of pulmonary vascular walls was due to an increase in relatively acellular fibrous or fibroelastic tissue. If the same underlying disease process is present in our case as in those of Taft and Mallory,[1] Smith and Kroop,[3] and Wade and

Ball,[2] and if cellular proliferation precedes fibrosis as in other vascular disorders, then in our case the cellular endothelial proliferation in the small muscular arteries and arterioles would represent earlier changes than previously described.

The necrotizing arteritis restricted to the muscular pulmonary arteries from 250 to 500 microns in diameter is interpreted as an acute response to a high degree of pulmonary hypertension proximal to the major point of obstruction to pulmonary arterial blood flow, namely in the distal arteries and proximal arterioles. Thrombosis in these vessels is thought to be secondary to the arteritis. Arteritis was not found in other organs.

This patient suffered basically from a widespread disorder of the arteries and arterioles with marked exacerbation of vascular disease in the lungs. The morphologic findings are in part compatible with the hypothesis of Smith and Kroop[3] that the pulmonary hypertension is secondary to a recurrent arterial spasm similar to that causing the peripheral manifestations of Raynaud's disease. The muscular hypertrophy of the media, the occasionally observed concentric arrangement of smooth muscle nuclei, and the wrinkling of the elastic membranes of the small muscular arteries furnish morphologic evidence of vasospasm. These findings, however, may to some degree also represent compensatory changes in response to increased intravascular pressure. Complete resolution of the etiology of the pulmonary vascular changes in these cases, therefore, must await further studies.

Summary

A case of Raynaud's disease with autopsy is reported in which the clinical picture was dominated by pulmonary hypertension apparently unassociated with any significant pulmonary parenchymal disease. Microscopically cellular intimal proliferation of small pulmonary muscular arteries and arterioles was the most characteristic lesion. In several proximal medium-sized muscular arteries there was necrotizing arteritis with thrombus formation. Similar vascular lesions were not found in other organs, although generalized arteriosclerosis and arteriolosclerosis were present. The pulmonary vascular changes are thought to represent a local exacerbation of generalized vascular disease, but a specific etiology was not apparent.

Summario in Interlingua

Es reportate un caso de morbo de Raynaud con necropsia, in que le tableau clinic esseva dominate per hypertension pulmonar apparentemente non-associate con significative morbo pulmono-parenchymal. Microscopicamente, le proliferation cellular del intima in le arterias e le arteriolas del musculo pulmonar esseva le lesion le plus characteristic. In plure arterias muscular proximal de dimensiones intermediari, arteritis necrotisante con formation de thrombos esseva constatate. In altere organos nulle simile lesiones vascular esseva trovate, ben que arterio- e arteriolosclerosis generalisate esseva presente. Es opinate que le alterationes pulmono-vascular representa un exacerbation local de generalisate morbo vascular, sed nulle etiologia specific esseva apparente.

References

1. Taft, E. B., and Mallory, G. K.: Primary pulmonary vascular sclerosis. Arch. Path. 42: 630, 1946.
2. Wade, G., and Ball, J.: Unexplained pulmonary hypertension. Quart. J. Med. 26, 83, 1957.
3. Smith, W. M., and Kroop, I. G.: Raynaud's disease in primary pulmonary hypertension. J.A.M.A. 165: 1245, 1957.
4. Schumacher, E. E., Jr.: Cor pulmonale in association with Raynaud's disease. Report of a case with sympathectomy. Henry Ford Hosp. Bull. 5: 256, 1957.
5. Chobanian, A. V., Halperin, M., and Hollander, W.: The mechanism of effort syncope in primary pulmonary hypertension. In preparation.
6. Heath, D., and Edwards, J. E.: The pathology of hypertensive pulmonary vascular disease. A description of 6 grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. Circulation 18: 533, 1958.

The Precordial Electrocardiogram during Exercise

By Ramon F. Abarquez, M.D., Alvin H. Freiman, M.D., Fredric Reichel, M.D., and John S. LaDue, M.D., Ph.D.

CONTINUOUS recording of the precordial electrocardiogram *during* vigorous exercise has been tested in 150 persons through the use of a new lead system, a new method of electrode attachment, and special types of electrodes and electrode paste. This technic has resulted in tracings that are almost free of skeletal muscle potentials and baseline shift in subjects performing the Master's 2-step test.

Many studies of the electrocardiogram taken *after* the completion of exercise have been reported.[1-4] While much valuable information has been acquired from the postexercise electrocardiogram, the test has distinct limitations. The technic is not without hazard, since patients with heart disease may develop serious reactions before the completion of the exercise.[1,2] Consequently patients with abnormal resting electrocardiograms are not usually tested.

Continuous recording of the electrocardiogram during the actual performance of exercise may have the following potential advantages: significant changes may develop during but not after the exercise; the test can be terminated at the first evidence of definite electrocardiographic abnormality or perhaps safely continued beyond any limits previously prescribed; the prompt recognition and timing of the earliest electrocardiographic manifestations of ischemia or arrhythmia permit greater flexibility in the amount of exercise employed; the relationship of pain and other cardiovascular symptoms can be correlated with electrocardiographic abnormalities during exercise.

In the past, efforts at recording the electrocardiogram during exercise have either modified the activity to secure interpretable tracings, employed lead systems that give unconventional patterns, or used electronic filters.[5-8] Figure 1 illustrates the artifacts seen in an electrocardiogram taken in the conventional fashion during mild exercise.

A system is described for monitoring the electrocardiogram during exercise that gives tracings almost free of muscle interference and baseline deflection, employs equipment now in general use, results in electrocardiograms comparable with precordial leads taken with the Wilson central terminal, and permits comparison with data compiled in the study of Master's postexercise tracings.

Materials and Method

Two types of electrodes were made. The right ear electrode consisted of a 2 by 2 cm.^{2} stainless-steel wire mesh (no. 80 and 0.0055 inch thick) connected to a plug jack.* The chest electrode was made of 1-cm. diameter stainless-steel wire mesh within a rubber tube 4 mm. thick and 1 cm. in diameter connected to a plug jack.* This was an adaptation described by Rowley et al.[10] The chest electrode was held in place by a foam rubber cushion 2.5 by 6 by 9 cm. with a hollowed-out area (1 cm. in diameter and 1 cm. deep) in the center (fig. 2). Electrode-to-skin contact was made with a bentonite electrode compound† similar to the electrode paste used in electroencephalography. The electrocardiograms were recorded on a 4-channel electrocardiograph.‡

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Supported by grant no. 87203 of the American Heart Association and by grant H-1978 of the National Institutes of Health, U. S. Public Health Service.

*RCA plug jack-phono input.

†Medcraft Electronic Corporation electrode paste (resistance 200 ohms), Catalog No. 773. Babylon, N. Y.

‡Sanborn Poly Viso Recorder 150, the Sanborn Co., Cambridge, Mass.

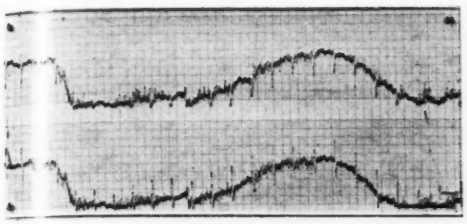

Figure 1

Skeletal muscle potentials and baseline deflections produced during exercise with the conventional lead system.

All subjects tested were clinically evaluated for cardiovascular disease and were advised not to eat or smoke 2 hours prior to the test. The standard 12-lead electrocardiogram was recorded at rest in a standing position. The precordial electrocardiogram during exercise was recorded by using a new system of electrode attachment. The ear electrode was secured to the right ear lobe by adhesive tape and a paper clip. Contact was made through the electrode paste. The chest electrodes were filled over the brim with the electrode compound and placed over the ensiform process, over the fifth rib in the V_3 position, the sixth rib in the V_5 position, and the seventh rib in the V_7 position. Each cupped electrode was held in place by a "band-aid" tape* and a foam rubber cushion. The wires leading to the plug jacks were taped to the skin. The foam rubber cushions were held in place over the electrodes by tightly wound elastic chest straps. The male portion of the patient cables was inserted into the plug jack. The right arm, left arm, left leg, and ground cables were attached to the right ear, ensiform, V_7, and right arm electrodes respectively. Precordial cables "B" and "C" were attached to the V_3 and V_5 electrodes respectively when the 4-channel electrocardiograph was used. With a single-channel machine the attachments were the same except that the left leg cable was attached to the V_5 electrode and the single precordial cable to the V_3 electrode. The patient cables and plug jacks were held in place by an elastic bandage and the free portions of the patient cables by another elastic strap wound around the waist. The precordial leads Ve, V_3, V_5, and V_7 were recorded by use of the appropriate position of the lead selector switch. Patients performed the single or double 2-step test as described by Master[1, 9] holding the cables with the right hand. Continuous recording of the precordial electrocardiogram was made on paper at a speed of 25 mm. per second.

*Band-Aid Plastic Strips, Johnson and Johnson, New Brunswick. N. J.

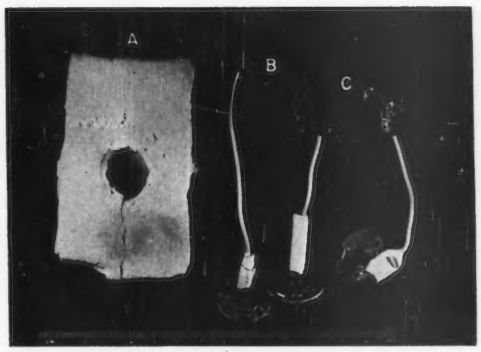

Figure 2

(a) Foam rubber cushion, (b) ear lobe wire mesh electrode, and (c) chest cupped-wire-mesh electrodes.

A paper speed of 50 mm. per second was used in some instances of extreme tachycardia. At the termination of exercise recording was continued for 30 seconds and then conventional Ve, V_3, V_5, and V_7 leads were recorded at 1, 2, 4, and 6 minutes with the subject standing.

Results

One hundred and fifty patients have had electrocardiograms taken during exercise. Almost all of the tracings were relatively free of wandering baseline and muscle interference so that exact measurement was possible of the amplitude and duration of all complexes (fig. 3). Movements of running, jumping, hyperventilating, or bending the trunk forward, backward, or sideways failed to alter significantly the excellence of the tracings.

Artifacts have been encountered when patients were steadied or given help while climbing the steps, when there was poor skin-to-electrode contact due to loose connections, when the electrodes slipped, when the patient's elbow struck the electrode attachments, when there was a retroflexed xiphoid process, and in women with pendulous breasts. In order to avoid muscle tremor and baseline shift during the actual performance of exercise, special attention should be given to the following points. The skin should be free of hair and cleansed well with alcohol. The ensiform should be exactly located and the electrode carefully placed upon the ensiform. In the

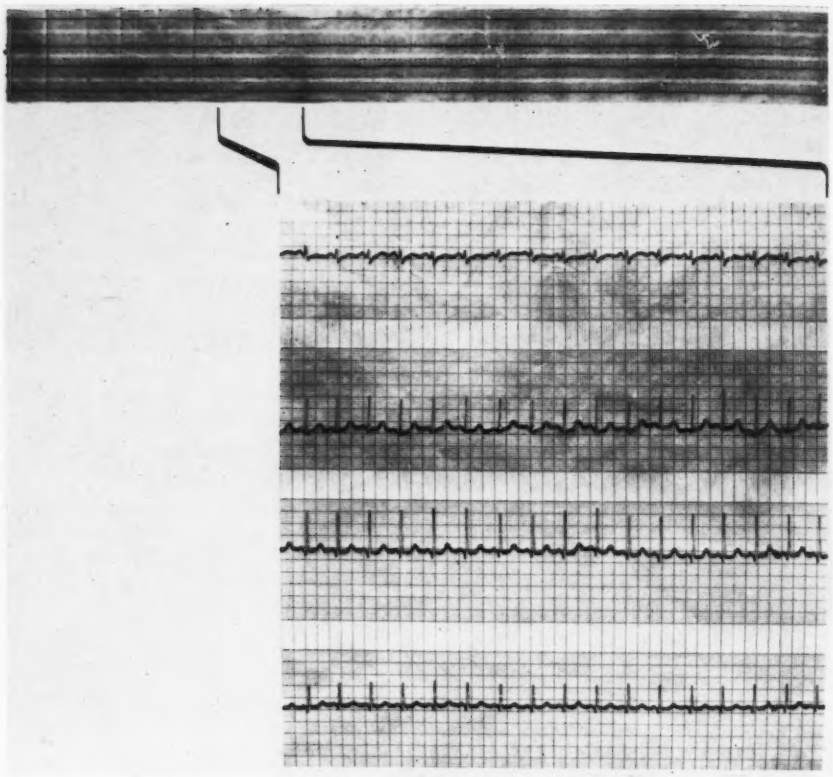

Figure 3

Continuous 1½ minute electrocardiogram taken during the two-step test demonstrates the absence of baseline shift. Magnified area shows the absence of muscle interference.

absence of the ensiform process the technical excellence of the tracings cannot be assured, but in these instances the ensiform electrode is placed on the fifth rib along the right sternal margin. The other precordial electrodes should be placed over the ribs and not in the intercostal spaces. The tip of the patient cable should be cleaned with sandpaper and attached securely to the plug jack. To insure good conduction, fresh electrode paste should be used for each test. All the attachments should be checked and loose connections localized by tugging on each cable and tapping each electrode attachment. The absence of baseline deflection indicates proper electrode placements. During the performance of the test the patient should not strike any of the electrode attachments with his swinging arms. The subject should not be touched or steadied during the test period.

The precordial tracings obtained by the conventional and the new lead systems were almost identical in vertical, intermediate, and horizontal electrical heart positions both before and after exercise (fig. 4). Tracings in the standing and recumbent positions were nearly identical in the RS-T segments and only minimal differences were apparent in the T waves.

The ST-segment alterations were maximal in leads V_3 and V_5 during and near the end of exercise but 90 per cent of these changes start to revert toward control levels within 5 to 30 seconds after termination of exercise.

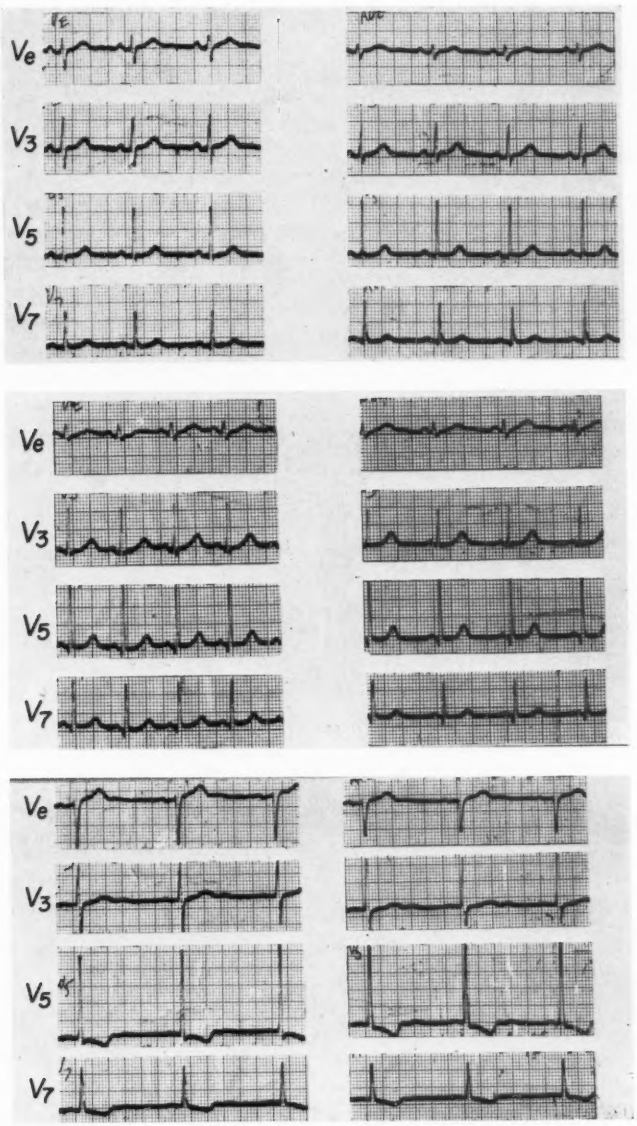

Figure 4

Similarity of the precordial leads obtained by the standard (left) *and E-E-P lead* (right) *systems in a vertical,* (top) *intermediate,* (middle) *and horizontal* (bottom) *electrical position of the heart.*

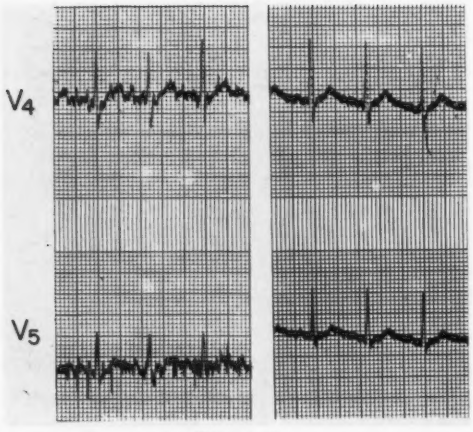

Figure 5

Leads V_4 and V_5 in a patient with Parkinsonism taken with standard technic (left) and with the new electrodes (right), electrode paste, and lead placement.

Discussion

According to Master and Rosenfeld[11] the maximal electrocardiographic alteration occurs in the tracings 2 minutes after exercise. The usual tracings taken immediately after and up to 2 minutes after exercise gave technically poor tracings because of tachypnea. These electrocardiograms were associated with wandering of the baseline that made accurate interpretation difficult. Our results show that the changes are greatest near the end of exercise and usually persist to a lesser degree thereafter. With the use of the special electrodes and electrode paste standard postexercise tracings have no baseline shift or muscle artifacts. This observation indicates that wandering of the baseline observed with tachypnea or hyperventilation is due to poor electrode-to-skin contact. With our system the only effect of tachypnea or hyperventilation was minor variation in the amplitudes of the QRS complexes.

Another use of the special electrodes and electrode paste was in patients suffering from Parkinsonism, delirium tremens, or chills in whom it was impossible to obtain interpretable tracings with the conventional leads and lead attachments. In such instances the special cupped electrodes filled with the bentonite electrode compound were placed on both acromion processes, the first lumbar vertebrae, and over the ribs at the position of the precordial leads desired. The left and right arm cables were connected respectively to the electrodes on the left and right acromial processes, while the left leg cable was attached to the lumbar vertebral electrode. Figure 5 shows the absence of muscle potentials in the electrocardiograms obtained with this system in a patient with Parkinsonism. The unipolar and bipolar leads obtained by this method were similar to the electrocardiograms obtained with the standard electrode attachments.

Preliminary findings with regard to the clinical application of this technic in obtaining information not otherwise available in the postexercise tracings include the following illustrative cases:

Case Reports

1. Sinus Tachycardia and ST-Segment Changes

A 26-year-old Negro woman with no history of cardiovascular, infectious, or psychogenic disease (presumably a normal person) performed the 2-step test for 3 minutes. At the one hundred and twentieth second of exercise the ST-segment was depressed by 2 mm., with a rate of 170 per minute. At the one hundred and seventy-fifth second of exercise and until the termination of the test the ST-segment was depressed by 2 mm. in V_5, the ST-segment was flat and the rate was 175 per minute. Tracings did not show the same changes.

These findings suggest that the electrocardiographic abnormalities were related to the degree of tachycardia and that the maximum heart rate during exercise should be considered before determining the "abnormality" of the test. If the test had been done in the conventional manner, these findings would not have been recorded.

2. Marked Changes during Exercises but Minimal Changes after Exercise (fig. 6)

A tracing was obtained from a 57-year-old white man with a history of angina of several years' duration and mild hypertension. A previous postexercise 2-step test in 1951 was interpreted as "probably positive" and a 12-lead standard electrocardiogram was within normal limits. During the double 2-step test, continuous monitoring of the electrocardiogram revealed the onset of ST-segment depression of 1.5 mm. in V_5 at 70 seconds. The depression gradually increased to a maximum of 4 mm. at 2½ minutes, remaining constant at

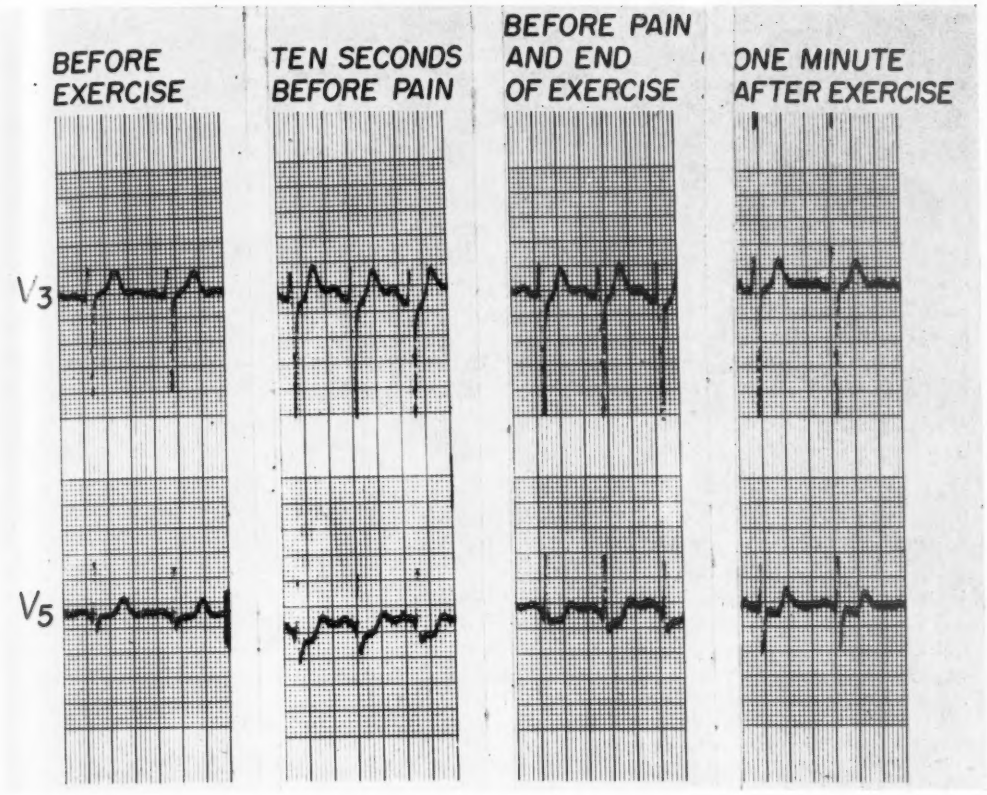

Figure 6

Coronary artery disease associated with marked electrocardiographic changes during exercise preceding pain and minimal electrocardiographic changes 1 minute after exercise.

that level for the remaining 30 seconds of exercise. At the end of exercise, the patient first noted retrosternal oppression relieved by rest. Within 30 seconds after termination of exercise, the ST-segment depression in V_5 had lessened to 1 mm., and within 1 minute, the "J" point had become isoelectric. In these postexercise tracings, however, the ST-segment sloped downward in V_5.

Significant ST-segment depression occurred 110 seconds before the appearance of pain. The dissociation of pain and electrocardiographic changes is not new. What is important is that during the performance of an exercise test the appearance of "ischemia" in the tracing may permit the termination of the test before the onset of pain. The rapid return within 30 seconds to 1-mm. depression of the ST-segment and to the isoelectric line at 1 minute after exercise makes the postexercise tracing questionably "positive." The 4-mm. ST-segment depression during the test would undoubtedly be considered definite evidence of ischemia by all present criteria.[13]

An interesting finding during the continuous monitoring of the electrocardiogram during exercise is the cyclic ebb and flow trend of the initial ST-segment changes. As the exercise continues the ST-segment changes become constant. This was a common observation in the electrocardiograms with "ischemic patterns" during exercise.

3. Early Onset and Persistent "Ischemic Changes" Without Pain (fig. 7)

A 58-year-old white woman had hypertensive cardiovascular disease without angina but with frequent episodes of paroxysmal atrial fibrillation. She had grade II retinopathy and left ventricular hypertrophy on x-ray and on the electrocardiogram. Medication included 1 mg. of reserpine, 1 Gm. of chlorothiazide daily, and sedation.

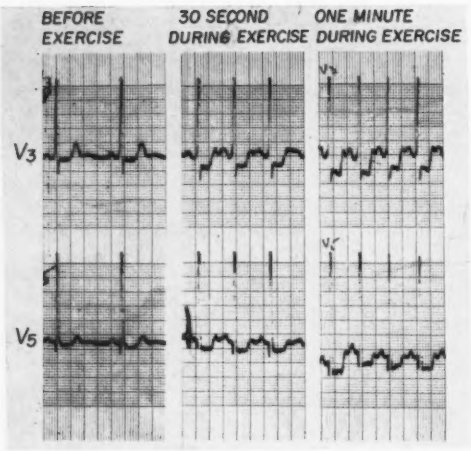

Figure 7
Early onset of "ischemic changes" during exercise.

During the thirtieth second of exercise, the ST-segment in V_3 and V_5 were depressed 3.5 and 2.5 mm. respectively. The depression gradually increased to a maximum of 5 mm. in V_3 and V_5 at the end of the test. The tracing 1 minute after exercise showed ST-segment depressions of 3 mm. in Ve, 5 mm. in V_3, and 4 mm. in V_5. At no time did the patient experience pain.

The marked ST-segment changes occurred very shortly after the onset of exercise, and the performance of even the single 2-step test was carried on in the presence of electrocardiographic evidence of severe ischemia. The ability to record the electrocardiogram during exercise would permit early termination of exercise, since continuance of the test in this patient beyond the thirtieth second of exercise would have been unnecessary.

4. Evaluation of Exercise Tolerance after Myocardial Infarction

A 48-year-old white man had a diaphragmatic wall myocardial infarction in 1955, persistent hypercholesteremia and occasional chest pain relieved by nitroglycerin. His resting electrocardiogram showed incomplete right bundle-branch block and a healed diaphragmatic wall infarct. He completed 3 minutes of exercise without developing pain or electrocardiographic changes (fig. 8).

Another patient, a 57-year-old white man, had a myocardial infarct in October 1957, and now complains of angina requiring 2 to 3 nitroglycerin tablets daily. He takes 0.1 mg. of digitoxin daily. During the seventieth second of exercise ST-segment depression developed that persisted throughout the remaining 20 seconds of exercise, but was not accompanied by chest pain (fig. 9). Although the electrocardiographic changes may represent myocardial ischemia, the influence of digitalis on the development of these ST-segment changes warrants further study. [12, 14]

These 2 cases illustrate a difference in response to exercise after myocardial infarction. It should again be pointed out that without continuous monitoring during the exercise many investigators would hesitate to employ the 2-step test on such patients.

Comment

In order to avoid any confusion regarding nomenclature, it is suggested that all electrocardiographic recordings obtained after termination of exercise be termed "postexercise electrocardiograms" and all electrocardiograms obtained during the actual performance of work or exercise be designated as "dynamic-exercise electrocardiograms."

For convenience we have modified our procedure without sacrificing data obtainable from the original method as follows:

1. The standard 12-lead electrocardiogram is taking standing at rest.
2. Precordial V_3 and V_5 tracings are done with the new system every 30 seconds during exercise or until significant changes appear. Then the recording is continued until the end of the test.
3. The exercise is terminated at the onset of significant electrocardiographic changes, chest pain, or other symptoms.
4. At the end of exercise the tracing is continued for 30 seconds and then recorded at 1, 2, 4, and 6 minutes with the subject standing at rest.

Conclusions

A technic has been described for recording the electrocardiogram *during* vigorous exercise with use of special electrodes, electrode paste, and electrode placement that we have designated as the "Ear-Ensiform-Precordial (E-E-P) system." Tracings during exercise relatively free of baseline shift and muscle interference have been obtained in 150 patients.

The procedure offers the advantage of safety, since exercise can be stopped at the first electrocardiographic evidence of abnormality or perhaps safely continued beyond

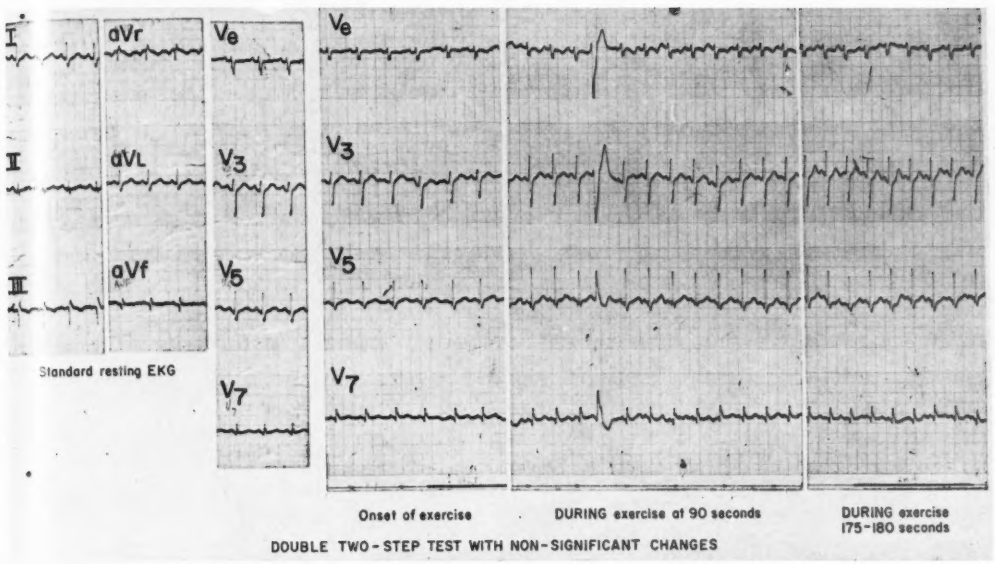

Figure 8

Absence of electrocardiographic changes during the double 2-step test in a patient with previous diaphragmatic myocardial infarction.

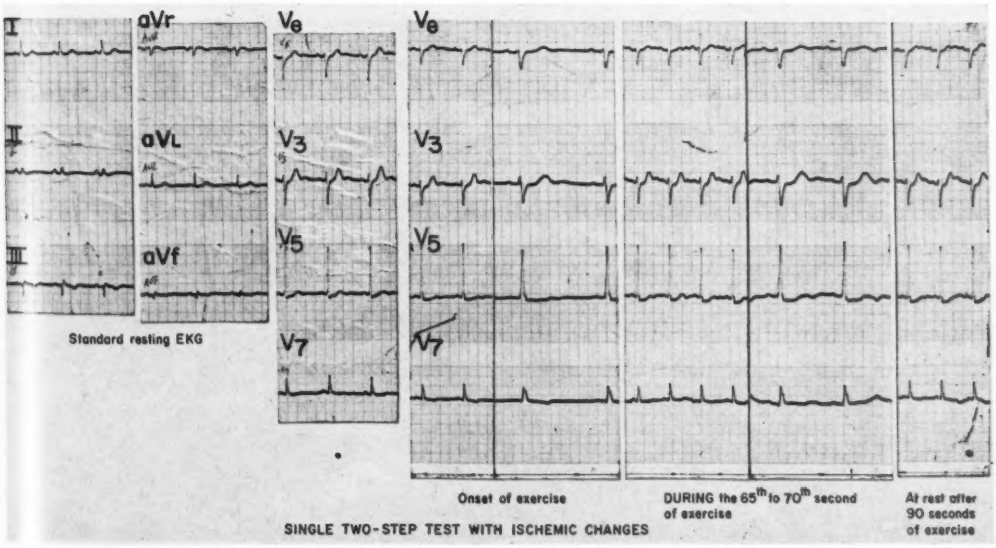

Figure 9

ST-segment changes during the single 2-step test in a patient with previous diaphragmatic myocardial infarction.

any limits previously described. The test can be done with any electrocardiograph without additional elect onic equipment.

The precordial tracings obtained by the E-E-P system are comparable to those obtained with the Wilson central termina'. The absence of significant baseline shift and muscle artifacts in the dynamic-exercise and post-exercise electrocardiograms permits exact study of the precordial electrocardiogram *during* and after exercise.

The technic makes possible detection of relatively transient electrocardiographic abnormalities that may be present *during* but not after exercise.

Acknowledgment

We wish to express our appreciation to Miss Louise Wecker for her technical assistance.

Summario in Interlingua

Es describite un technica pro le registration del electrocardiogramma durante vigorose exercitio, con le uso de electrodos special, pasta electrodic, e un placiamento del electrodos que nos ha designate como le "systema auro-ensiformo-precordial." Registrationes durante exercitio relativemente libere de migration del linea de base e de interferentia muscular esseva obtenite in 150 patientes.

Le technica ha l avantage de esser innocente, proque le exercitio pote esser interrumpite al prime signo electrocardiographic de un anormalitate. Illo etiam pote esser continuate salvemente in ultra del limites previemente describite. Le test pote esser executate con non importa qual electrocardiographo, sin ulle equipamento electronic additional.

Le registrationes precordial obtenite per medio de iste systema es comparabile a illos obtenite con le terminal central de Wilson. Le absentia de un significative migration del linea de base e de interferentias muscular in le electrocardiogramma de exercitio dynamic e post-exercitial permitte un studio exacte del electrocardiogramma precordial durante e post exercitio.

Le technica rende possibile le detection de relativemente transiente anormalitates electrocardiographic le quales es presente durante sed non post le exercitio.

References

1. MASTER, A. M., AND OPPENHEIMER, E. T.: A simple exercise tolerance test for circulatory efficiency with standard tables for normal individuals. Am. J. M. Sc. **177**: 223, 1929.
2. SIMONSON, E., AND KEYS, A.: The electrocardiographic exercise tests. Am. Heart J. **52**: 83, 1956.
3. BROUHA, L., GRAYBIEL, A., AND HEATH, C. W.: The step test, a simple method of measuring physical fitness for hard muscular work in adult man. Rev. Canad. Biol. **2**: 86, 1943.
4. GRAYBIEL, A., AND ALLEBACH, N. W.: The work electrocardiogram. Am. J. Cardiol. **3**: 430, 1959.
5. Registration of the electrocardiogram in workers during labor in industry. Bull. Eksp. Biol. Med. Suppl. **43**: 59, 1957.
6. BENGTSSON, E.: The exercise electrocardiogram in healthy children and in comparison with adults. Acta med. Scandinav. **154**: 225, 1956.
7. KATTUS, A. A., LONGMIRE, W. P., CANNON, J. A., WINFIELD, M. E., AND DAVIS, J. H.: Diagnostic and functional evaluation of candidates for endarterectomy. Arch. Int. Med. **104**: 870, 1959.
8. FREIMAN, A. H., TOLLES, W., CARBERY, W., RUEGSEGGER, P., ABARQUEZ, R., AND LADUE, J. S.: The electrocardiogram during exercise. Am. J. Cardiol. **5**: 506, 1960.
9. MASTER, A. M., FIELD, L. E., AND DONOSO, E.: Coronary artery disease and the two-step test. New York State J. Med. **57**: 1051, 1957.
10. ROWLEY, D. A., GLAGON, S., AND STONER, P.: Measurement of human heart rate during usual activity. Science **130**: 976, 1959.
11. MASTER, A. M., AND ROSENFELD, I.: Master two-step exercise test. J.A.M.A. **172**: 265, 1960.
12. SCHERF, D.: Development of the electrocardiographic exercise test. Am. J. Cardiol. **5**: 433, 1960.
13. MASTER, A. M., AND DONOSO, E.: A symposium: the two-step exercise test. Heart Bull. **8**: 62, 1959.
14. LIEBOW, I. M., AND FEIL, H.: Digitalis and the normal work electrocardiogram. Am. Heart. J. **22**: 683, 1941.

The Mammary Souffle of Pregnancy and Lactation

By BERNARD TABATZNIK, B.Sc., M.B., M.R.C.P., THOMAS W. RANDALL, M.D. (Witwatersrand), AND COLIN HERSCH, DIP. MED. (Witwatersand)

IN 1908 van den Bergh[1] described a loud systolic murmur of unusual quality that appeared in a woman the day after parturition. It was localized to a small area in the second right intercostal space, and disappeared entirely when firm pressure with the stethoscope bell was applied over the site of maximum intensity. He believed the murmur was extracardiac, and owed its origin to enlarged tortuous branches of the internal mammary artery. In an extensive study of women during pregnancy and the puerperium he found 13 instances of such a murmur.

Fresh interest in the origin and mechanism of this extracardiac murmur has recently developed.[2-9] Scott and Murphy[7] introduced the term *mammary souffle* to describe the murmur, since they considered the mechanism similar to that of the uterine souffle.

We have recently encountered several examples of a mammary souffle in patients referred with such diagnoses as patent ductus arteriosus, aortic stenosis with regurgitation, and ventricular septal defect. The diagnostic difficulties created by these cases stimulated the following investigation into the incidence and clinical features of the mammary souffle.

Methods and Material

A total of 257 women were examined during pregnancy and the puerperium. The cases were distributed as follows: 19 patients in the first trimester of pregnancy, 28 patients in the second trimester, 45 patients in the third trimester, 165 patients in the first 2 weeks of the puerperium.

Phonocardiograms were recorded in 12 patients, with use of a Sanborn Twin-Beam Cardiette and electrocardiographic monitor. Logarithmic recordings were taken with a medium-sized open bell or a diaphragm chest piece, at paper speeds of 75 mm. per second with vertical timing markers at 0.04 and 0.20 second. The frequency response of this instrument reaches 500 cycles per second in the high-frequency range.

The response of the murmur to posture, respiration and the Valsalva maneuver was observed.

Results

Incidence

Twenty-five of 165 patients (15.3 per cent) examined in the postpartum period had a mammary souffle. The murmur was first heard between the second and tenth postpartum days in all instances, usually between the second and the fifth days. One patient who had given birth to a stillborn fetus showed the murmur on the second postpartum day. She was treated with stilbestrol and the murmur disappeared 2 days later. In patients who continued to lactate, the murmur remained audible for several weeks, and in 1 patient it persisted for 10 weeks after parturition. Parity did not influence the incidence of the murmur.

In the smaller series of patients examined during pregnancy the murmur was present in 6 of 45 cases in the third trimester (13.3 per cent), 5 of 28 in the second trimester (17.9 per cent), and in none in the first trimester.

Site

The murmur was maximal in the second right intercostal space in 9 patients, in the second left intercostal space in 14 patients, in the third left intercostal space in 4 patients, in the fourth left intercostal space in 3 patients, and in both second intercostal spaces in 6 patients. The murmur radiated poorly and was not heard in the neck or the back. Palpable arterial pulsation in the relevant intercostal spaces was noted in most cases.

Graphic Features

Examples of the murmur are illustrated in figure 1. The murmur was confined to systole

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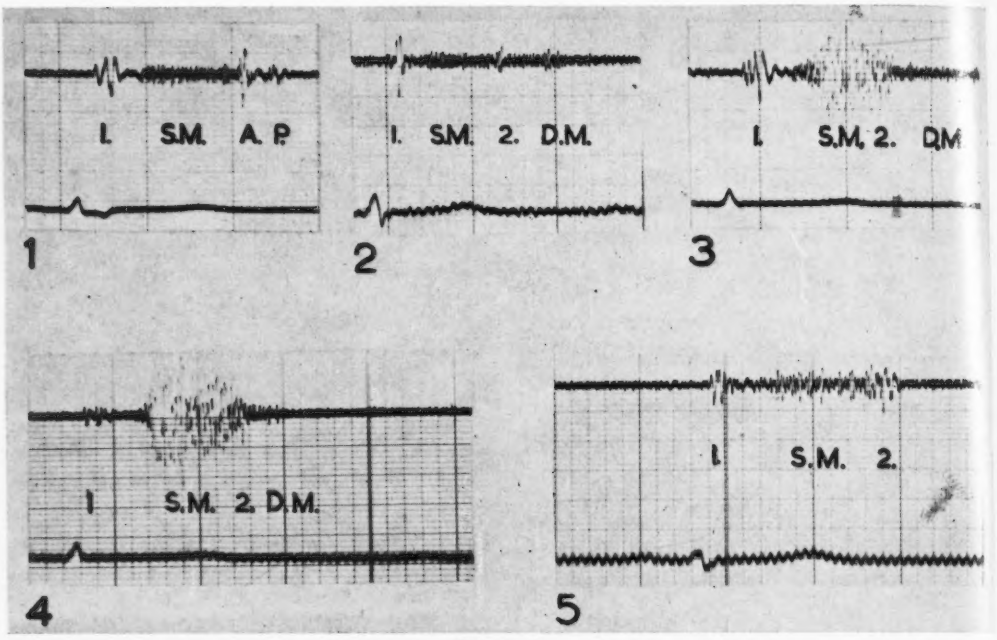

Figure 1

Phonocardiograms (1—5) of 5 patients illustrating the mammary souffle. Note: (a) delay in onset of the systolic murmur, (b), high-frequency vibrations of the systolic murmur, (c) continuous murmur in tracing 2, (d) spill-over into early diastole in tracings 3 and 4. 1, first heart sound; 2, second heart sound; S.M., systolic murmur; D.M., diastolic murmur; A, aortic component of second heart sound; P, pulmonary component of second heart sound.

in some instances (e.g., 1 and 5 in fig. 1). In the majority of cases, however, a short diastolic element was present as well (e.g., 3 and 4 in fig. 1). In some cases it continued through most of the cardiac cycle (e.g., 2 in fig. 1). In all instances an interval was present between the first heart sound and the commencement of the murmur, which extended up to or beyond the second heart sound. The vibrations responsible for the murmur were generally of very high frequency, so that it was often difficult to obtain satisfactory phonocardiographic records unless the murmur was loud.

The murmur could be obliterated either by direct compression with the stethoscope (fig. 2) or by firm pressure over the relevant intercostal space with the finger placed *lateral* to the stethoscope bell. It varied considerably in intensity not only from day to day, but in some instances from beat to beat. There was no clearcut relationship between engorgement of the breasts immediately prior to suckling and intensity of the murmur. It was always heard best with the patient lying flat, and sometimes disappeared completely when the patient sat up. Respiration had little effect on the murmur. The Valsalva maneuver diminished its intensity but did not effect its disappearance.

Associated Heart Disease

Six of the 36 patients with a mammary souffle had toxemia of pregnancy with hypertension. One other patient had severe puerperal megaloblastic anemia with dextrocardia and situs inversus; a continuous murmur was present in the second right intercostal space; compression obliterated this murmur, but a

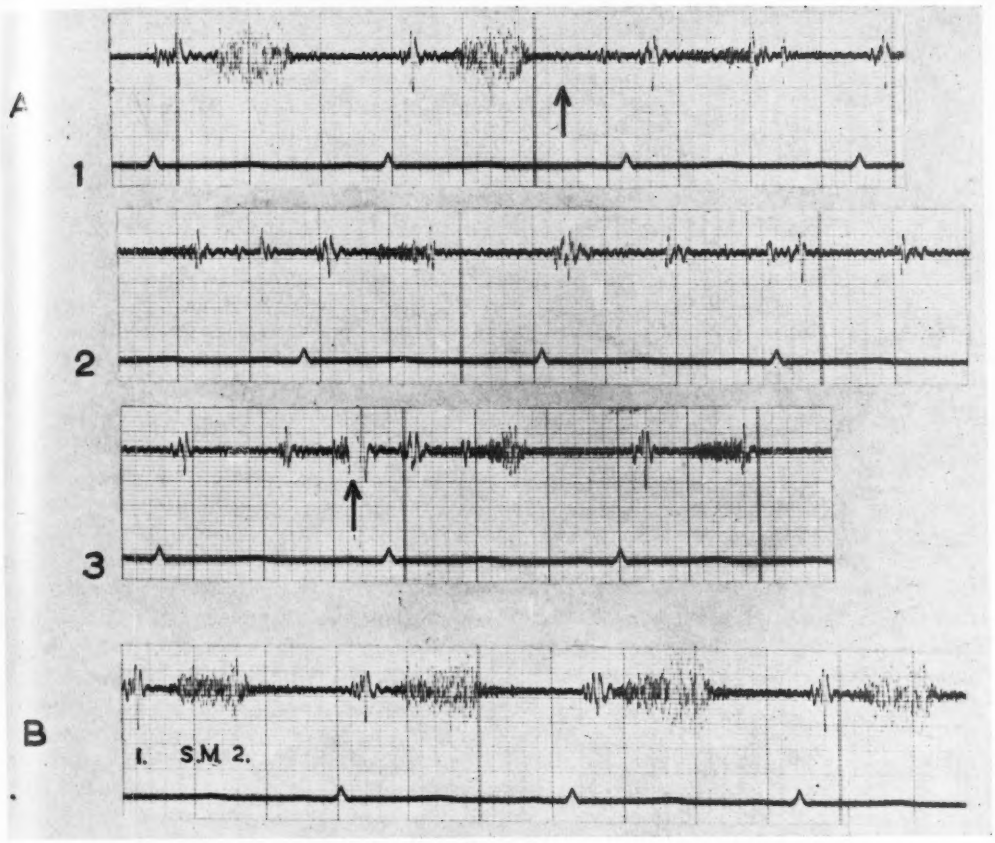

Figure 2

A. Phonocardiogram (continuous strip) recorded in the fourth left intercostal space, showing high-frequency late systolic murmur that disappeared after compression with the stethoscope bell (arrow in strip A1). The murmur reappears after release of compression (arrow in strip A3). B. *Recorded 30 seconds after* A, *showing return of the murmur to its previous intensity.*

midsystolic ejection type murmur of moderate intensity persisted. No patient was encountered with rheumatic valvular disease and a mammary souffle.

Four electrocardiograms were abnormal, showing left bundle-branch block, right bundle-branch block, atrioventricular block of the Wenckebach type, and the features of dextrocardia.

Of the 18 postpartum patients in whom chest radiography was performed, 10 were normal, 3 showed prominence of the pulmonary artery segment, and 5 were found to have a cardiothoracic ratio ranging between 50 and 56 per cent. The apparent cardiomegaly could not be explained by elevation of the diaphragm. Three of these patients showed a normal cardiothoracic ratio 6 months after delivery.

Discussion

The differential diagnosis of the mammary souffle has been discussed in detail by Scott and Murphy.[7] Patent ductus arteriosus is the most prevalent form of congenital heart disease encountered in pregnancy.[10] It may be difficult to distinguish the continuous murmur

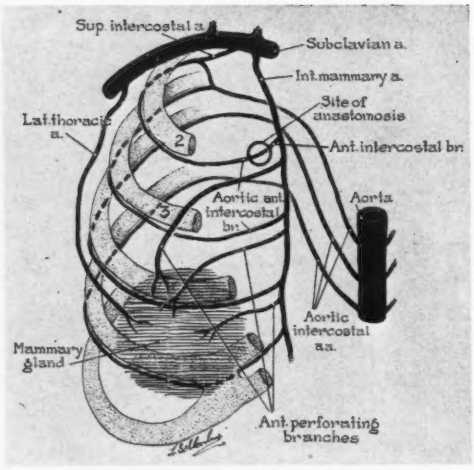

Figure 3

Semi-diagrammatic representation of the arterial blood supply to the breast.

of this condition from the mammary souffle under circumstances where the circulatory effects of pregnancy, with high pulse pressure and apparent cardiomegaly, may be similar to those found in patent ductus arteriosus. Obliteration of the mammary souffle by compression should differentiate it from the murmur of patent ductus arteriosus as well as from the murmurs of combined aortic stenosis and insufficiency. The mammary souffle that is confined to systole is readily distinguished from the innocent ejection systolic murmur of pregnancy[8] by its late systolic accentuation and its response to compression.

The exact mechanism of the souffle has not been established. Our observations are consistent with the view of Scott and Murphy,[7] McKusick,[9] and others[1, 3, 5] that it is arterial in origin. Hurst, Staton, and Hubbard,[6] on the other hand, considered that the continuous murmur in one of their cases arose in the dilated superficial veins of the breast. The graphic features of the murmur, with high-frequency vibrations, delay in onset, and late systolic accentuation, are those of an arterial bruit. By contrast, the vibrations of a venous hum are coarse and of low frequency, and show an early diastolic accentuation. The possibility that the souffle originates in arteriovenous communications within the breast is considered unlikely, since the murmur is most frequently heard in the second intercostal spaces at some distance from the breast. Failure of the Valsalva maneuver to abolish the murmur and the presence of prominent arterial pulsations in the underlying intercostal spaces lend added support to the arterial origin of the murmur.

The breast has an abundant arterial blood supply, which is provided by the internal mammary artery, the aortic intercostal arteries, and the lateral thoracic artery[11] (fig. 3). The degree of participation of these vessels varies greatly and is seldom symmetrical. The perforating branches of the internal mammary artery are the most important and constant of these arteries. The second, third, and fourth branches become greatly enlarged during lactation.[12] Van den Bergh's view, therefore, that the mammary souffle arises in these enlarged tortuous vessels[1] seems most acceptable, notwithstanding Jensen's statement in 1938 that such an explanation for the murmur is "justly consigned to oblivion."[2]

As Hurst, Staton, and Hubbard[6] point out, however, the obliteration by digital compression applied lateral to the site of the murmur is not adequately explained by the above hypothesis. Since the perforating arteries run in a lateral direction toward the breast, the murmur should disappear after medial rather than lateral compression.

This inconsistency may be explained by attributing a significant role in the genesis of the mammary souffle to the intercostal arteries. The aorta supplies anterior intercostal branches to the lower 10 intercostal spaces and occasionally to the second intercostal space as well. The first 2 intercostal spaces are supplied by the superior intercostal artery, a branch of the costocervical trunk of the subclavian (fig. 3). The anterior and collateral branches of these aortic intercostal arteries anastomose extensively with the anterior intercostal branches of the internal mammary artery.[12] It is conceivable that during pregnancy and lactation considerable

amounts of blood are diverted toward the breasts along the perforating branches of the mammary artery. Lesser amounts of blood may therefore flow along the anterior intercostal branches of the internal mammary artery. This could create a pressure gradient between the anterior branches of the aortic intercostal arteries (or the superior intercostal artery in the second intercostal space) and the anterior intercostal branches of the internal mammary artery (fig. 3). The mammary souffle may be the consequence of such an alteration in dynamics and could thus arise at the site of anastomosis between these two vessels. This could account for its localization to a restricted area, its lack of radiation, its disappearance on lateral compression in the corresponding intercostal space, and the frequent association of prominent intercostal pulsation.

Summary

Two hundred and fifty-seven consecutive South African Bantu women were examined during pregnancy and the puerperium in order to determine the incidence of the mammary souffle. It was found in 15.3 per cent of women examined in the postpartum period, 13.3 per cent in the third trimester of pregnancy, 17.9 per cent in the second trimester, and in none before the twelfth week of pregnancy.

The phonocardiographic features of the murmur are illustrated and evidence is presented to indicate that the murmur is arterial in origin.

It is suggested that the murmur may arise at the site of anastomosis between branches of the aortic intercostal arteries and branches of the internal mammary artery.

Summario in Interlingua

Esseva examinate 257 consecutive feminas bantu de Sud-Africa durante le pregnantia e le puerperio pro determinar le incidentia de sufflo mammari. Le sufflo esseva incontrate in 15,3 pro cento del feminas durante le periodo post parto, in 13,3 pro cento durante le tertie trimestre del pregnantia, in 17,9 pro cento durante le secunde trimestre, e in nulle ante le dece-secunde septimana del pregnantia.

Le characteristicas phonocardiographic del murmure es illustrate, e datos es presentate que indica que illo es de origine arterial.

Es formulate le hypothese que le murmure prende su origine in le sito de anastomoses inter brancas de arterias intercostal aortic e brancas del arteria interne mammari.

References

1. VAN DER BERGH, A. A. H.: Een schijnbaar Hartgeruisch. Nederl. tijdschr. geneesk. 52: 1104, 1908.
2. JENSEN, J.: The Heart in Pregnancy. St. Louis, C. V. Mosby Co., 1938, p. 83.
3. JONES, A. M.: Heart Disease in Pregnancy. London, Harvey and Blythe Limited, 1951, p. 11.
4. GILSTON, R. J., AND MCPHAUL, J. J.: Physiologic murmurs in pregnancy: a re-emphasis. M. Ann. District of Columbia 24: 461, 1955.
5. GRANT, R. P.: A precordial murmur of extracardiac origin during pregnancy. Am. Heart J. 52: 944, 1956.
6. HURST, J. W., STATON, J., AND HUBBARD, D.: Precordial murmurs during pregnancy and lactation. New England J. Med. 259: 515, 1958.
7. SCOTT, J. T., AND MURPHY, E. A.: Mammary souffle of pregnancy: Report of two cases simulating patent ductus arteriosus. Circulation 18: 1038, 1958.
8. BRAUN, K., YODFAT, Y., WEISSKOPF, E., AND SADOWSKY, E.: The phonocardiogram of the innocent murmur of pregnancy. Israel M. J. 17: 253, 1958.
9. MCKUSICK, V. A.: Cardiovascular Sound in Health and Disease. Baltimore, Williams & Wilkins Co., 1959, p. 234.
10. ESPINO-VELA, J., AND CASTRO-ABREU, D.: Congenital heart disease associated with pregnancy. Am. Heart J. 51: 542, 1956.
11. MALINIAC, J. W.: Arterial blood supply of the breast: revised anatomic data relating to reconstructive surgery. Arch. Surg. 47: 329, 1943.
12. PATTEN, B. M.: *In* Morris' Human Anatomy. Edited by J. Parsons Schaffer. Ed. 11. New York and Toronto, The Blakiston Co., 1953, p. 671; p. 692.

Comparative Studies of Protoveratrine A and Protoveratrine B Intravenously in Hypertensive Man

By BERTRAM M. WINER, M.D.

VERATRUM ALKALOIDS are powerful hypotensive agents with many desirable characteristics,[1-3] but the usefulness of the available preparations has been limited by a narrow dosage range between hypotensive and emetic effects. After the physicochemical separation of some of the alkaloids had been accomplished,[4] a search for an alkaloid with a wider spread between hypotensive and emetic doses was undertaken. Parenteral studies in dogs demonstrated that the hypotensive activity of protoveratrine A was slightly greater than that of protoveratrine B, but did not show differing degrees of dissociation of hypotensive from emetic activity.[5] A comparison between protoveratrine A and protoveratrine B in man, however, revealed marked differences when the alkaloids were administered orally: protoveratrine A had strong hypotensive activity but a narrow therapeutic dosage range, whereas protoveratrine B required much larger doses to elicit hypotensive effects but had a wider range between hypotensive and emetic effects.[6-8] These differences prompted a comparative study of the responses of hypertensive patients to intravenous administration of the 2 alkaloids.

Material and Methods

Comparative bioassays of protoveratrine A and protoveratrine B were obtained in 13 patients who were known to have essential or renal hypertension, sustained despite the oral or intravenous administration of placebos. At least 4 different hypotensive doses of each alkaloid were given intravenously to each subject. The largest dose given to each patient was determined by the production of a fall in blood pressure to or less than normal or by nausea or vomiting. Protoveratrine A was given on 81 occasions, protoveratrine B on 109. No more than 1 study was conducted in a given patient on the same day. Each alkaloid was administered in a measured period of 2 minutes. With the patient in the recumbent position, a technician determined blood pressure and pulse rate at intervals of a few minutes during periods of at least 20 minutes before and several hours after administration. Blood pressure was measured by the auscultatory technic according to the criteria of the American Heart Association. Mean blood pressure was calculated as the diastolic pressure plus one third of the difference between systolic and diastolic pressures. The mean value of the lowest 2 mean blood pressures obtained within 25 minutes after administration of an alkaloid was taken as the maximal response to the given dose of the alkaloid. These responses were used to construct logarithmic dose-response curves. The occurrence and severity of paresthesias, nausea, and vomiting were noted. Electrocardiograms were taken during studies of the larger doses and whenever bradyeardia was marked.

Observations of the effects of protoveratrine B intravenously were made an additional 48 times in 21 other adult hypertensive patients. This information was used with the above to estimate the dose of protoveratrine B required to produce a fall in blood pressure to 150/100 mm. Hg or less.

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Supported by grant no. H-1835 from the National Institutes of Health, U. S. Public Health Service.

Results

Qualitative Similarities

Each alkaloid had strong hypotensive and bradycrotic activity, and each was capable of inducing nausea or vomiting. The occurrence and magnitude of these effects varied with the amount of alkaloid given (table 1), but the time of onset and duration of the effects were similar for the 2 alkaloids.

The first effect was the occurrence within several minutes of paresthesias, sensations of warmth or burning, which were noted sequentially in the throat, chest, perineum, and extremities. Brief sneezing was common. The paresthesias regressed within 30 to 60 minutes.

Systolic and diastolic blood pressure began to fall a few minutes after administration of the drugs with maximal response within

1: to 25 minutes. Blood pressure was maintained at the lower levels for 45 to 90 minutes (fig. 1). Return to control values occurred in approximately 3 hours.

Pulse rate usually decreased slightly during the hypotensive action of both alkaloids. Marked sinus bradycardia, however, of less than 48 beats per minute occurred in 5 patients after each alkaloid. At rates of approximately 40 beats per minute, the site of impulse formation varied between the sinoatrial and atrioventricular nodes in the course of consecutive beats or groups of beats for periods of minutes. During the height of the bradycardia ventricular or supraventricular premature beats, at times in bigeminal fashion, were occasionally seen. The T waves in leads V_4, V_5, and V_6 were transiently inverted in several patients. All of these effects, the sinus bradycardia, atrioventricular rhythm, premature beats, and T-wave inversions, were immediately reversible by administration of 0.4 to 1.0 mg. of atropine sulfate intravenously, usually without affecting the blood pressure response (fig. 2).

At the height of the paresthesias, approximately 10 minutes after drug administration, a tight sensation in the chest and epigastrium was occasionally noted after the larger doses of either alkaloid. This pain forewarned nausea with or without vomiting and hiccoughs. Emetic responses lasted less than a half hour.

Table 1

Responses of a Representative Subject, A. D., to Intravenous Protoveratrine A and Protoveratrine B

Protoveratrine A								Protoveratrine B							
Control		Dose		Response				Control		Dose		Response			
Blood pressure mm. Hg	Pulse rate	μg.	μg./Kg.	Blood pressure mm. Hg	Pulse rate	Paresthesias*	Nausea*	Vomiting	Blood pressure mm. Hg	Pulse rate	μg.	μg./Kg.	Blood pressure mm. H	Pulse rate	Paresthesias*	Nausea*	Vomiting
201/120	76	0†	0	200/118	76	0	0	0	205/118	92	0	0	197/119	84	0	0	0
196/119	84	50	0.7	192/120	80	*	0	0	185/108	90	50	0.7	177/108	84	*	0	0
204/122	80	100	1.4	179/111	68	*	0	0	194/114	76	100	1.4	178/110	72	**	0	0
203/117	86	100	1.4	173/103	76	**	0	0	191/116	84	130	1.9	172/106	76	**	0	0
182/112	76	125	1.8	145/95	64	**	0	0	195/117	80	160	2.3	157/98	72	**	0	0
205/123	78	145	2.1	147/99	60	***	*	0	198/115	84	175	2.5	148/97	76	**	0	0
193/113	84	150	2.2	122/76	64	***	**	0	184/113	80	200	2.9	125/81	76	**	0	0
200/118	76	160	2.3	130/80	64	***	**	0	185/111	84	215	3.1	130/83	76	**	0	0
197/119	76	175	2.5	135/89	72	***	***	V	182/110	73	230	3.3	106/69	72	***	0	0
179/118	76	175	2.5	124/89	75	***	***	V	197/121	84	250	3.6	109/72	76	***	0	0
									200/121	76	250	3.6	112/68	72	***	0	0
									191/115	96	250	3.6	116/76	76	***	0	0
									199/118	84	270	3.9	124/77	76	***	*	0
									197/119	78	300	4.3	98/68	74	***	**	0

*Graded * to ***, slight to marked.
†At 0 dose, 2 ml. of saline intravenously.

Quantitative Differences

For a considerable portion of the dose ranges given to 10 subjects, there was a linear relation between hypotensive response and the log dose in each case. These data were used for the estimation of the relative hypotensive potencies of the 2 substances (table 2, columns 1 and 2). On a weight basis protoveratrine B was slightly less potent (82 per cent) than protoveratrine A.

A dose producing nausea was reached in 10 patients with protoveratrine A (table 2, column 3). Vomiting occurred in 7 of these patients. Nausea was produced in 6 patients after protoveratrine B, vomiting in 3. The emetic doses of protoveratrine B were .24,

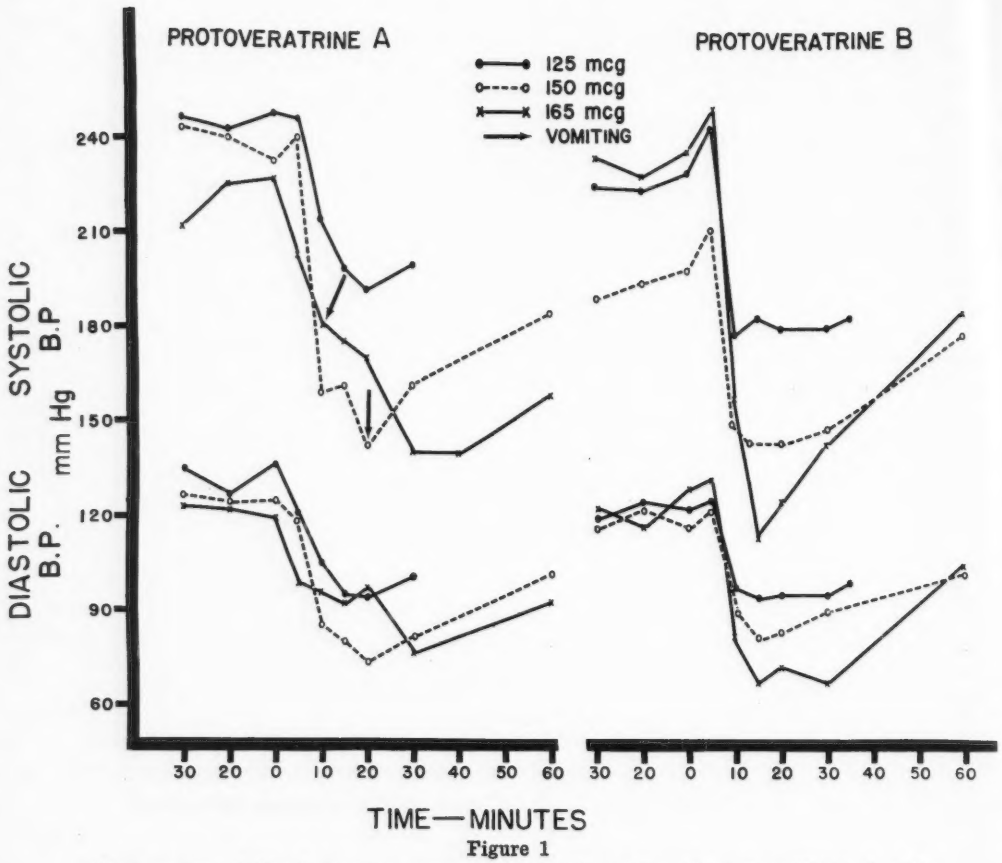

Figure 1

Time course of blood pressure response to varying doses of protoveratrine A and protoveratrine B.

.25, and .38 mg., equivalent to 2.9, 4.4, and 4.6 μg per Kg. The vomiting induced by protoveratrine B occurred after doses that produced subnormal blood pressures. Following normotensive doses of protoveratrine A, small increases in dose induced nausea and vomiting, and a diminished blood pressure response (fig. 3). In contrast, in the same patients subnormal blood pressure could be achieved by protoveratrine B without an emetic response. The remarkable reproducibility of the response of an individual to a given dose of intravenous veratrum is also evident in this figure.

Protoveratrine B had less emetic activity than protoveratrine A at equipotent hypotensive doses. A statistical comparison of the hypotensive and emetic activities of the 2 alkaloids (table 2) was obtained by determination of tolerance ratios in which the largest doses of protoveratrine B given without nausea were compared with the doses of protoveratrine A producing nausea. These ratios were adjusted for the differences in hypotensive potency of the alkaloids. Protoveratrine B was better tolerated than protoveratrine A ($p < .001$).

Optimal Dose of Protoveratrine B

The doses of protoveratrine B that lowered the blood pressure of 34 hypertensive patients to 150/100 mm. Hg or less are indicated in

Table 2

Relative Hypotensive and Emetic Potencies of Protoveratrine A and Protoveratrine B

Patient	Hypotensive potency ratio Protoveratrine B/protoveratrine A: Estimate	95% Confidence limits	Dose of A producing nausea μg./Kg.	Maximum dose of B without nausea μg./Kg.	Tolerance ratio Col (4) ÷ Col (3)	Effective tolerance ratio Col (1) x Col (5)	Significance of difference: Col (6) from 100%
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
DG	74%	65-86	2.42	4.15	171%	127%	$p<.01$
DF	102%	86-124	3.13	4.66	148%	151%	$p<.001$
JC	71%	64-79	3.24	5.04	156%	111%	$p<.05$
FK	76%	56-103	2.75	4.95	180%	137%	$p<.05$
SG	74%	63-84	—	3.64	—	—	—
IR	91%	72-101	—	2.47	—	—	—
JR	65%	54-77	—	3.01	—	—	—
MB	95%	87-104	2.51	3.87	154%	147%	$p<.001$
AD	79%	71-89	2.07	3.58	173%	137%	$p<.001$
HF	95%	84-107	1.44	2.31	161%	153%	$p<.01$
CW	—	—	2.22	3.70	167%	—	—
BK	—	—	2.95	3.85	131%	—	—
IF	—	—	2.43	4.37	180%	—	—
Geometric mean	82%	—			161%	138%	$p<.001$
95% Confidence limits	73-98				150-173	124-152	

figure 4. Total single doses of .15 to .20 mg. (1.8 to 3.0 μg./Kg) were effective in 28 patients. It is likely that some of these patients required less, but received doses in this range after recognition that such doses were both strongly hypotensive and well tolerated. Interestingly, the patient who required the smallest dose per kilogram was a strikingly obese woman, and the subject requiring the largest dose was a poorly nourished man.

Discussion

Protoveratrine A and protoveratrine B are tetraesters of the alkamine, protoverine. They differ by a single hydroxyl group in one of the acids[4] (table 3).

The hypotensive effect is largely a reflex action, which originates in the heart (Bezold-Jarisch effect), carotid sinus, and lungs.[9-15] The receptors transmit impulses to the vasomotor center by the vagi and carotid sinus nerves. Vasodilatation is the result of changes in the transmission of vasoconstrictor nerve impulses.[16, 17] Efferent vagal activity is increased, largely reflexly. Cardiac output is variably affected.[18, 19] Cerebrovascular[20] and renal resistances[21] decrease.

The emetic action appears to be a reflex effect that originates in or near the nodose ganglion.[22] The veratrum alkaloids do not directly stimulate the vomiting center nor the chemoreceptor trigger zone.[23]

The dissociation between the hypotensive and emetic activities of the tetraesters of veratrum may be ascribed to differences in the accessibility of the receptors or to intrinsic differences in the receptors themselves at the different sites of hypotensive and emetic action. The degree of the dissociation of activities appears to be influenced by the chemical configurations of the alkaloids.

Protoveratrine B had less emetic activity than protoveratrine A at doses causing equivalent hypotensive effects in hypertensive man

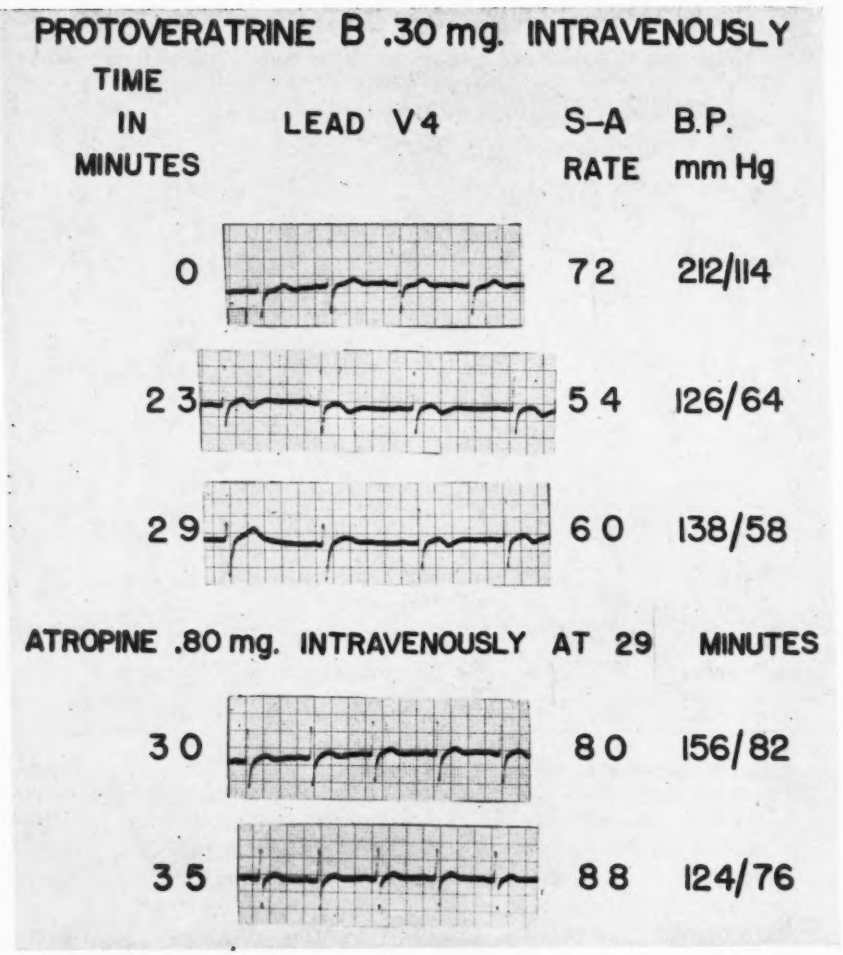

Figure 2

Protoveratrine B-induced sinus bradycardia, intermittent A-V nodal rhythm (third strip), and T-wave inversions of the sinus beats in lead V_4. Atropine reversed the bradycardia and T-wave changes, although the hypotensive effect continued.

Table 3

Hydrolysis of Protoveratrine A and Protoveratrine B

Protoveratrine A	Protoveratrine B
$C_{41}H_{69}O_{14}N$	$C_{41}H_{69}O_{15}N$
↓ Hydrolysis	↓ Hydrolysis
Protoverine	Protoverine
Acetic acid	Acetic acid
Acetic acid	Acetic acid
2-methyl butyric acid	2-methyl butyric acid
2-hydroxy-2 methyl butyric acid	2, 3-dihydroxy-2 methyl butyric acid

($p < .001$). In contrast to protoveratrine A, protoveratrine B had little emetic activity when given intravenously in doses producing normotension. Protoveratrine B appears to have properties that warrant its preferential use for parenteral administration.

The data in this bioassay demonstrated considerable precision. The 95-per cent confidence limits of both the hypotensive potency ratios and the tolerance ratios were relatively narrow. For example, the ratio of the upper

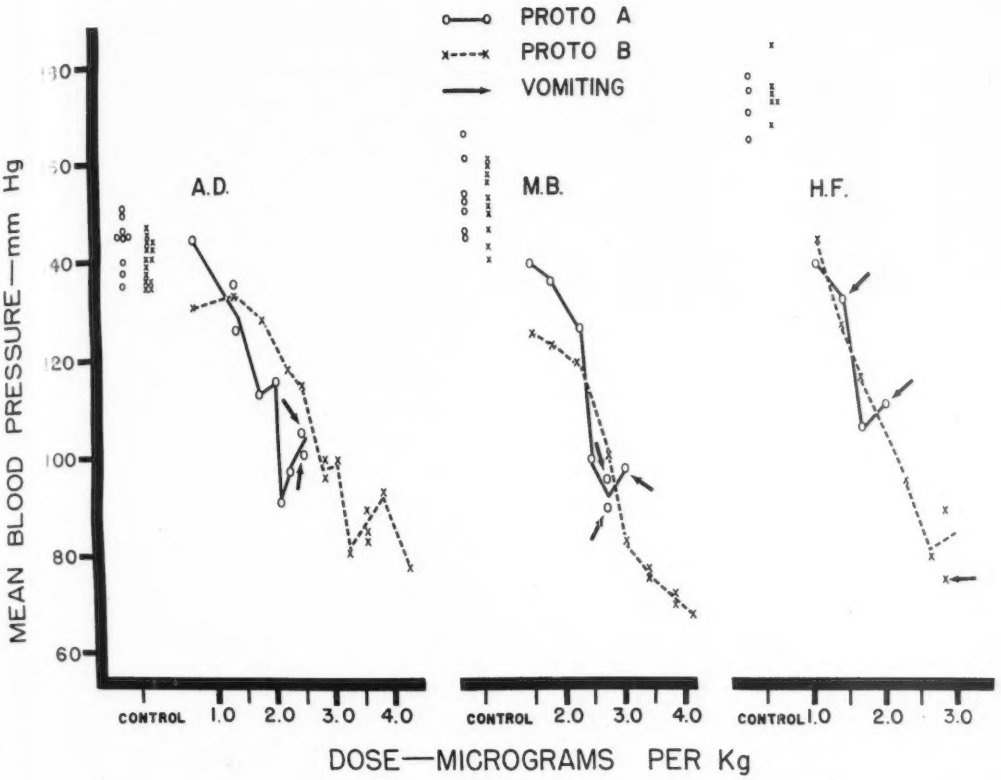

Figure 3

Dose-response curves of protoveratrine A and protoveratrine B in 3 hypertensive subjects. Emetic responses are indicated by arrows.

95 per cent limit to the lower 95 per cent limit of the hypotensive potency ratios was less than 150 per cent in 9 of 10 cases.

Protoveratrine B has qualities that favor its clinical use intravenously in hypertensive emergencies. Its potent vasodepressor and cardiodecelerator effects, as well as its development of maximal action within minutes, are particularly valuable in acute left ventricular failure and in eclampsia, acute glomerulonephritis, or malignant hypertension with hypertensive encephalopathy. Derivatives of Rauwolfia, administered intramuscularly, have been exceedingly useful in the management of urgent hypertensive problems, but in instances requiring a quick and strong hypotensive effect protoveratrine B may be preferable. Indeed, the two have been used together, protoveratrine B intravenously to achieve control within 10 to 15 minutes, and alkaloids of Rauwolfia intramuscularly to maintain it.

Orally protoveratrine A is the active alkaloid in mixtures of protoveratrines A and B.[6-8] Its long-term use is difficult because of a narrow range between hypotensive and emetic doses. Protoveratrine B can be an effective hypotensive agent when administered orally, but large doses have been required due to incomplete absorption or inactivation by the gastrointestinal tract or liver. The hypotensive effect of protoveratrine B orally tends to be prolonged; an emetic response has been rare. Mild neuromuscular effects, muscle tightness and muscle weakness, may be induced.

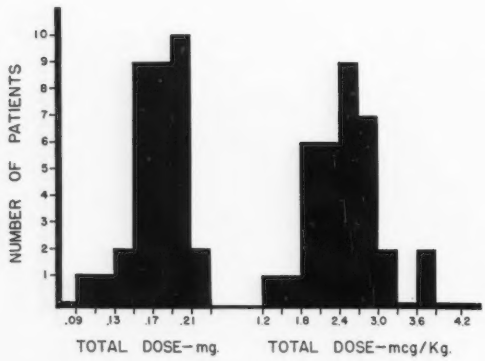

Figure 4

The total dose of protoveratrine B and the dose in micrograms per kilogram that reduces the blood pressure of 34 hypertensive patients to or below 150/100 mm. Hg. are plotted against the number of patients yielding the response.

The clinical use of tetraesters of veratrum appears to be safe. No deaths or vascular catastrophes have been ascribed to their use. An oral overdose of 75 times the recommended dose of a mixture of protoveratrines A and B was tolerated.[24] Excessive hypotension after parenteral administration is rare and can be overcome by the injection of 25 mg. of ephedrine sulfate intramuscularly or by other vasoconstrictor agents. Intravenous administration of atropine sulfate in doses of 0.4 to 1.0 mg. abolishes undesired vagal effects on heart rate and rhythm, usually without loss of the hypotensive response.[25-27] The transient T-wave inversions induced by veratrum in the left precordial leads resemble those observed in anxious patients during hyperventilation.[28, 29] In both cases the T-wave changes can be reversed by vagolytic agents.

Although biologic assay technics are uncommonly used in man, fixed hypertension lends itself to their application. The virtues of such technics in human pharmacology have been demonstrated in studies of digitalis glycosides[30] and diuretics.[31] Comparative bioassays in stable clinical disease states foster the perception of clinically significant differences among drugs that are chemically closely related.

Summary

Comparative studies of intravenously administered protoveratrine A and protoveratrine B in hypertensive man indicate that the alkaloids have qualitatively similar hypotensive, bradycrotic, and emetic actions, but quantitatively different hypotensive and emetic potency. The relative hypotensive potencies of the two substances were determined by analyses of logarithmic dose-response curves in the same patients. On a weight basis protoveratrine B was slightly less potent than protoveratrine A.

A favorable dissociation between hypotensive and emetic activity was found. Tolerance ratios were determined in which the largest doses of protoveratrine B given without nausea were compared with the doses of protoveratrine A producing nausea. These ratios were adjusted for the differences in hypotensive potency of the alkaloids. Protoveratrine B was better tolerated than protoveratrine A ($p < .001$). Indeed, protoveratrine B had little emetic activity when given intravenously in doses producing normotension. Protoveratrine B appears to have properties that warrant its preferential selection for parenteral administration. Its effective dosage range has been studied.

The strong hypotensive activity of intravenously administered protoveratrine B, its development of maximal action within minutes, and its pulse-slowing effect favor its use in those hypertensive states in which almost immediate lowering of the blood pressure is indicated.

Fixed hypertension lends itself to the application of biological assay technics. The use of such technics in human pharmacology fosters the perception of clinically significant differences among drugs that are chemically closely related.

Acknowledgment

I am indebted to Miss Margaret McDonough for technical assistance, to Dr. Mindel C. Sheps of the Department of Public Health, Harvard Medical School, for the helpful analyses, to Dr. Otto Krayer for his statistical criticism, and to Dr. Phillip Boyer of the Pitman-Moore Company for generous supplies of the alkaloids.

Summario in Interlingua

Studios comparative de protoveratrina A e de protoveratrina B, administrate per via intravenose in humanos hypertensive, indica que le alcaloides ha qualitativemente simile effectos hypotensive, bradycardiac, e emetic, sed que lor potentias hypotensive e emetic es quantitativemente differente. Le relative potentias hypotensive del duo substantias esseva determinate per analyses del curvas logarithmic de dose e responsa in le mesme patientes. Super le base de pressiones equal, protoveratrina B esseva levemente minus potente que protoveratrina A.

Un dissociation favorabile inter le activitate hypotensive e le activitate emetic esseva constatate. Proportiones de tolerantia esseva determinate in que le dosis maximal de protoveratrina administrate sin subsequente nausea esseva comparate con le doses de protoveratrina A que produceva tal nausea. Iste proportiones esseva adjustate pro le differentias in le potentia hypotensive del duo alcaloides. Protoveratrina B esseva melio tolerate que protoveratrina A (p minus que 0,001). De facto, protoveratrina B habeva pauc activitate emetic quando illo esseva administrate intravenosemente in doses producente normotension. Protoveratrina B pare haber proprietates que justifica su selection preferential pro administrationes parenteral. Su gamma de dosage efficace esseva studiate.

Le forte activitate hypotensive de protoveratrina B in administration intravenose, le facto que illo disveloppa su effecto maximal intra alicun minutas, e su effecto relentatori super le pulso es rationes pro recommendar su uso in le statos de hypertension in le quales un reduction quasi immediate del tension de sanguine es indicate.

Hypertension fixe se presta al application de technicas de essayage biologic. Le uso de tal technicas in le pharmacologia human promove le perception de clinicamente significative differentias inter drogas que es chimicamente affin.

References

1. Krayer, O., and Acheson, G. H.: The pharmacology of the veratrum alkaloids. Physiol. Rev. **26**: 383, 1946.
2. Meilman, E., and Krayer, O.: Clinical studies on veratrum alkaloids. II. The dose-response relations of protoveratrine in hypertension. Circulation **6**: 212, 1952.
3. Hoobler, S. W., Corley, R. W., Kabza, T. G., and Loyke, H. F.: Treatment of hypertension with oral protoveratrine. Ann. Int. Med. **37**: 465, 1952.
4. Nash, H. A., and Brooker, R. M.: Hypotensive alkaloids from veratrum album, protoveratrine A, protoveratrine B and germitetrine B. J. Am. Chem. Soc. **75**: 1942, 1953.
5. Abreu, B. E., Richards, A. B., Alexander, W. M., and Weaver, L. C.: Cardiovascular, emetic and pharmacodynamic properties of certain veratrum alkaloids. J. Pharmacol. & Exper. Therap. **112**: 73, 1954.
6. Winer, B. M.: A comparison between protoveratrine A and protoveratrine B orally in arterial hypertension. New England J. Med. **255**: 1173, 1956.
7. —: Studies of two pure veratrum alkaloids, protoveratrine A and protoveratrine B. Circulation **14**: 1019, 1956.
8. —: Studies of pure veratrum alkaloids, protoveratrine A, protoveratrine B, and germitetrine B. Circulation **16**: 953, 1957.
9. Symposium on reflexes from the heart and lungs. XIX. International Physiological Congress, Montreal, 1953, p. 40.
10. Bezold, A. von, and Hirt, L.: Über die physiologischen Wirkungen des essigsauren Veratrins. Untersuch. a. d. physiol. Lab. Würzburg **1**: 73, 1867.
11. Jarisch, A., and Richter, H.: Die afferenten Bahnen des Veratrineffektes in den Herznerven. Arch. f. exper. Path. u. Pharmakol. **193**: 355, 1939.
12. Dawes, G. S.: Studies on veratrum alkaloids. VII. Receptor areas in coronary arteries and elsewhere as revealed by use of veratridine. J. Pharmacol. & Exper. Therap. **89**: 325, 1947.
13. Aviado, D. M., Jr., Li, T. H., Kalow, W., Schmidt, C. F., Turnbull, G. L., Peskin, G. W., Hess, M. E., and Weiss, A. J.: Respiratory and circulatory reflexes from the perfused heart and pulmonary circulation of the dog. Am. J. Physiol. **165**: 261, 1951.
14. Wang, S. C., Ngai, S. H., and Grossman, R. G.: Mechanism of vasomotor action of veratrum alkaloids: extravagal sites of action of veriloid, protoveratrine, germitrine, neogermitrine, germerine, veratridine, and veratramine. J. Pharmacol. & Exper. Therap. **113**: 100, 1955.
15. Gruhzit, C. C., Freyburger, W. A., and Moe, G. K.: Action of veriloid on carotid pressoreceptors. J. Pharmacol. & Exper. Therap. **109**: 261, 1953.
16. Krayer, O.: Untersuchungen über die Kreislaufwirkung der veratrum Alkaloide. Arch. f. exper. Path. u. Pharmakol. **209**: 405, 1950.
17. —, Moe, G. K., and Mendez, R.: Studies on veratrum alkaloids. VI. Protoveratrine: its comparative toxicity and its circulatory action. J. Pharmacol. & Exper. Therap. **82**: 167, 1944.
18. Hoobler, S. W., Kabza, T. G., and Corley, R. W.: The effect of protoveratrine on the cardiac output and on some regional circulations in man. J. Clin. Invest. **34**: 559, 1955.
19. Myers, G. S., Friedlich, A. L., Scannell, J. G., O'Neill, J. R., and Currens, J. H.: Cardiac catheterization studies of the action of protoveratrine on patients with left heart failure.

Proc. New England Cardiovas. Soc., Nov. 1952.
20. Crumptom, C. W., Klingensmith, W. C., Keffer, N. J., and Hafkenschiel, J. H.: Effects of protoveratrine on cerebral hemodynamics and oxygen metabolism in hypertensive subjects. Fed. Proc. 10: 32, 1951.
21. Meilman, E.: Clinical studies on veratrum alkaloids. III. The effect of protoveratrine on renal function in man. J. Clin. Invest. 32: 80, 1953.
22. Swiss, E. D.: The emetic properties of veratrum derivatives. J. Pharmacol. & Exper. Therap. 104: 76, 1952.
23. Borison, H. L., and Wang, S. C.: Physiology and pharmacology of vomiting. Pharmacol. Rev. 5: 193, 1953.
24. Currens, J. H., Myers, G. S., and White, P. D.: Use of protoveratrine in treatment of hypertensive vascular disease. Am. Heart J. 46: 576, 1953.
25. Meilman, E., and Krayer, O.: Clinical studies on veratrum alkaloids. I. The action of protoveratrine and veratridine in hypertension. Circulation 1: 204, 1950.
26. Elek, S. R., McNair, J. D., and Griffith, G. C.: The electrocardiographic effects of intravenous veratrum viride. Circulation 7: 903, 1953.
27. Margolin, E. G., Levine, H. D., and Merrill, J. P.: Cardiac arrhythmias associated with protoveratrine. Am. Heart J. 52: 257, 1956.
28. Wasserburger, R. H., Siebecker, K. L., and Lewis, W. C.: The effect of hyperventilation on the normal adult electrocardiogram. Circulation 13: 850, 1956.
29. Yu, P. N., and Yim, B. J.: Electrocardiographic changes in hyperventilation syndrome: Possible mechanism and clinical implications. Trr. A. Am. Physicians 71: 129, 1958.
30. Gold, H.: Digitalis and some of its derivatives. II. Science 97: 150, 1943.
31. Greiner, T., Gold, H., Ganz, A., Kwit, N. T., Warshaw, L., Rao, N., and Fujimori, H.: "Case Report" in human pharmacology. J.A.M.A. 171: 290, 1959.

A teacher I had in college, Professor Edwin B. Holt, once pointed out to me a fact of considerable bearing when one is dealing with abstract and collective nouns. "A word," he said, "that has many connotations can denote nothing; conversely, a word that denotes but one thing has no connotations." The word water, for example, has numerous connotations—"weak as water," "As the hart panteth after the water books," "as wet as water," etc.—but H_2O denotes but one thing and so has no connotations.

Now, it seems to me that part of the task of the poet or the essayist is to use the connotative words that exactly convey his feeling, whereas a part of the task of the scientist is to employ denotative words with comparable logical skill and verifiable precision—Alan Gregg, M.D. *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 100.

Tetralogy of Fallot with Anomalous Tricuspid Valve Simulating Pulmonary Stenosis with Intact Septum

By HENRY N. NEUFELD, M.D., DWIGHT C. McGOON, M.D., JAMES W. DUSHANE, M.D., AND JESSE E. EDWARDS, M.D.

THE anatomic[1-4] and clinical[5-7] features and the results of hemodynamic investigations[8-10] in the tetralogy of Fallot are now universally known. It has been emphasized that anatomic deviations in the degree of pulmonary stenosis or in the size of the ventricular septal defect may yield different patterns of clinical features and hemodynamics in this anomaly.

Recently, we observed 3 cases in which the clinical picture suggested severe pulmonic stenosis with an intact ventricular septum associated with a right-to-left shunt. However, cardiac catheterization showed that the shunt was at the ventricular level. It was demonstrated also that the right ventricular systolic pressure was significantly greater than the systolic pressure in systemic arteries. Therefore, it was assumed clinically that these cases were examples of severe pulmonary stenosis with a small ventricular septal defect.

Pathologic examination in one instance (case 1) and the anatomic findings at operation in the other two (cases 2 and 3) demonstrated that the ventricular septal defects were of the usual "large" size seen in the tetralogy of Fallot. In addition to these findings, however, an anomaly of the tricuspid valve was present in all 3 cases. This took the form of a flap of accessory valvular tissue that partially closed the ventricular septal defect during ventricular systole.

It is the purpose of this paper to illustrate the clinical and pathologic findings in these 3 cases. To the best of our knowledge, this anatomic entity has not been described previously in relationship to the associated alterations in hemodynamics.

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This study was aided in part by grant no. H-4014 from the National Heart Institute, U. S. Public Health Service.

Presentation of Cases

Since the findings were similar in all 3 patients, these are described together for the group. The clinical findings are summarized in table 1 and the hemodynamic data in table 2.

Clinical Data

The patients were 2 boys and a girl, aged 12, 5, and 7 years, respectively. Two had been cyanotic since early infancy, whereas cyanosis had been observed in the 7-year-old patient since the age of 5 years. There was no history of "squatting" in any of the patients. The main complaints were shortness of breath and changes related to reduced cardiac functional capacity. Clubbing of the digits and distended cervical veins were noted in each patient. One patient (case 1) had signs of severe congestive failure of the right side of the heart.

All 3 patients had a typical murmur of stenosis, with maximal intensity at the pulmonary zone, and a diminished nonduplicated (pure) second pulmonic sound. In case 1, a febrile illness had been present for several weeks in the immediate period before our observation; as judged from later studies, this probably represented an episode of bacterial endocarditis, although this specific diagnosis had not been made. Congestive cardiac failure began at the time of the febrile illness and was the cause of death in this patient. In cases 2 and 3, corrective operations were done with the aid of the bypass machine and extracorporeal circulation. In both of these cases, the postoperative course and follow-up studies indicated satisfactory results.

Radiologic and Electrocardiographic Findings (Fig. 1-3)

The radiologic examination showed slight to great enlargement of the heart. The pulmonary vasculature was diminished in each case. Evidence of poststenotic dilatation of the pulmonary artery was absent. In case 1, a right aortic arch was observed radiologically.

Electrocardiographically, each patient had a normal sinus rhythm. The P waves were peaked in lead II in all instances. Right axis deviation ranging from +100 to +150 degrees was observed. Signs of pronounced right ventricular hypertrophy were present in each.

Table 1

Clinical Data in Tetralogy of Fallot with Anomalous Tricuspid Valve

Case	Age (yr.) and sex	Cardiac functional capacity, N. Y. Ht. Class.	Right vent. impulse	Onset of cyanosis	Club-bing	Distended neck veins	Congest. heart failure	Systolic murmur	Pulmonic second sound
1	12 M	IV	Normal	Early infancy	+	+	+	Grade 2	Diminished pure
2	5 M	IV	Force-ful	Early infancy	+	+	—	Grade 2 to 3	Diminished pure
3	7 F	III	Force-ful	At 5 years	+	+	—	Grade 4	Diminished pure

Table 2

Physiologic Data in Tetralogy of Fallot with Anomalous Tricuspid Valve

	Cases		
	1*	2*†	3†‡
Average pressures, mm. Hg			
Right atrium	17/11	9	15/8 (11)
Right ventricle	138/5-15	160/1-20 208/12	212/15 226/7
Infundibulum	28/3	118/2-20	100/25
Pulmonary artery	18/9	—	—
Systemic artery	97/73	119/69 (fem. art.) 117/10 (left vent.)	115/75 95/70 (by cuff)
Average blood oxygen saturation, %			
Venae cavae	22	72	75
Right atrium	21	70	73
Right ventricle	23	71	72
Pulmonary artery	27	—	—
Systemic artery	38	90.6	86
Pulmonary flow, L./min.§	0.3	1.0	3.19
Pulmonary flow index, L./min./M.^{2}	0.4	1.9	—
Systemic flow, L./min.	3.8	1.9	—
Right-to-left shunt, % of systemic flow	88	47	—
Systemic flow index, L./min./M.^{2}	5	3.6	—

*Dye-dilution curves showed a right-to-left shunt at the ventricular level.

†Pressures obtained during operation.

‡Cardiac catheterization performed elsewhere.

§Calculation of pulmonary flow was based on the assumption that pulmonary venous blood is fully saturated; since the child was studied under balanced amnesia and analgesia, some degree of pulmonary venous desaturation may have been present.

Physiologic Findings

Cardiac catheterization was done in each case, and dye-dilution studies were made in 2. The results showed remarkable similarity among the 3 cases (table 2). We are indebted to Dr. C. R. Cumming, of Winnipeg, Manitoba, who kindly supplied the data obtained at cardiac catheterization in case 3.

The striking feature in all 3 cases was the increased right ventricular systolic pressure, which was significantly greater than the systemic pressure (fig. 4). The gradient of systolic pressure between the two systems ranged from 41 to 97 mm. Hg. In each case, the pressure tracings showed evidence for both valvular and infundibular stenosis. In case 1, this was established by measurements of infundibular and pulmonary arterial pressures. In the other 2 cases, the catheter did not enter the pulmonary trunk, but an infundibular chamber was assumed; here, the pressure

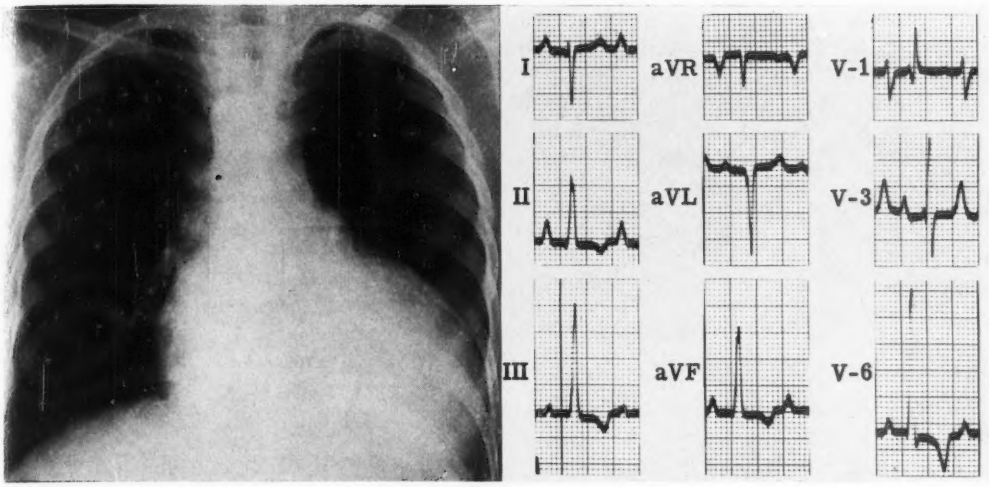

Figure 1

Case 1. Posteroanterior thoracic roentgenogram and electrocardiogram (see text for details).

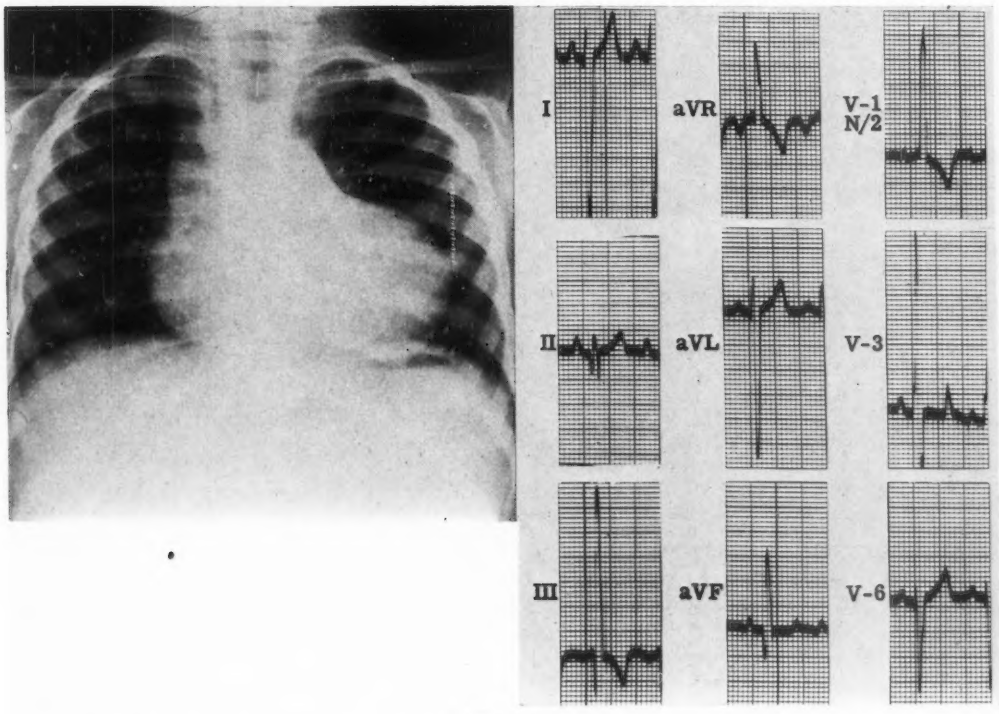

Figure 2

Case 2. Posteroanterior thoracic roentgenogram and electrocardiogram (see text for details).

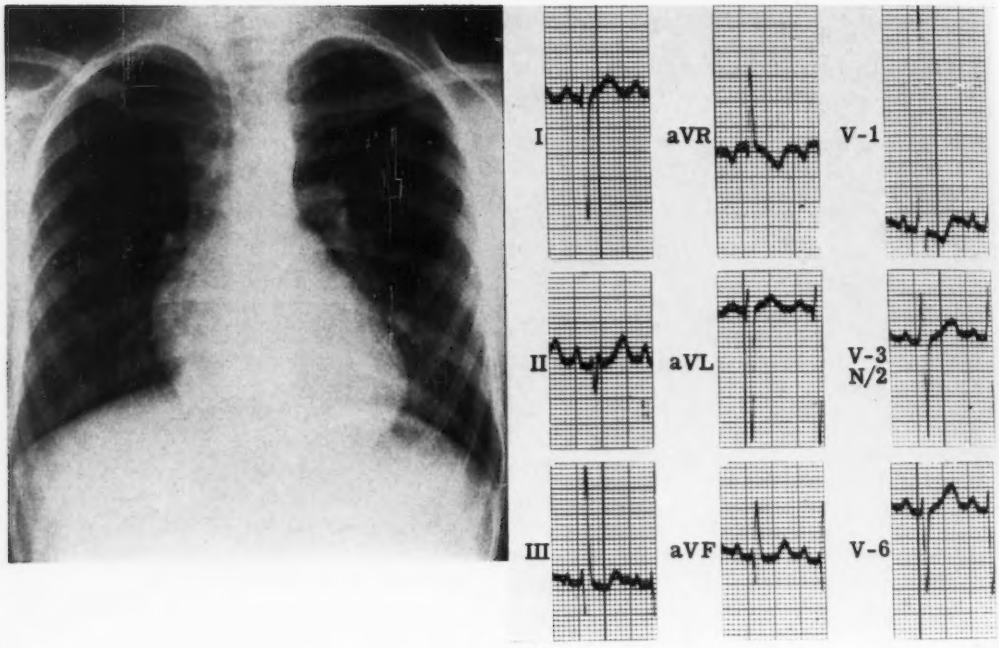

Figure 3

Case 3. Posteroanterior thoracic roentgenogram and electrocardiogram (see text for details).

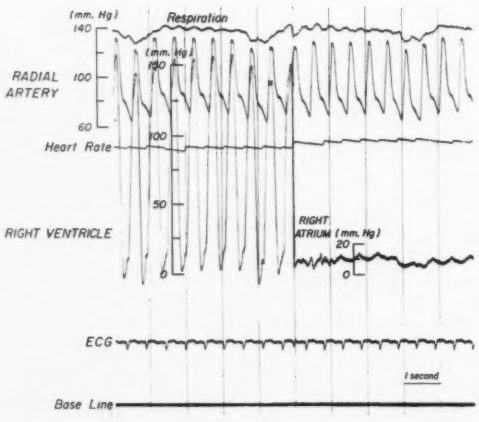

Figure 4

Case 2. Pressures obtained simultaneously within right ventricle and femoral artery, showing gradient in pressure between the two circulations, with the right ventricular pressure exceeding the systemic pressure.

was high but it was less than that in the main right ventricle. These observations were interpreted as reflecting stenosis at a point leading into the infundibular chamber and indicating severer stenosis at the exit of the chamber, the latter point most likely being the pulmonary valve.

Right atrial pressures were greatly increased in all 3 cases, and prominent "a" waves were noted. Pronounced peripheral oxygen desaturation was present in all cases. In the 2 patients (cases 1 and 2) in whom dye-dilution studies were performed, a right-to-left shunt was demonstrated at the ventricular level.

Pathologic Data

Case 1. The interior of the heart showed a large ventricular septal defect 1.6 cm. in diameter in the uppermost portion of the ventricular septum behind a hypertrophied and vertical crista supraventricularis. The crista divided the outflow tract of the right ventricle into a posterior subaortic channel and an anterior subpulmonary channel (fig. 5). The entrance to the latter was only 3 mm. in diameter. Above this, the infundibular subpulmonary chamber was dilated to a diameter of about 1.5 cm. The pulmonary valve was bi-

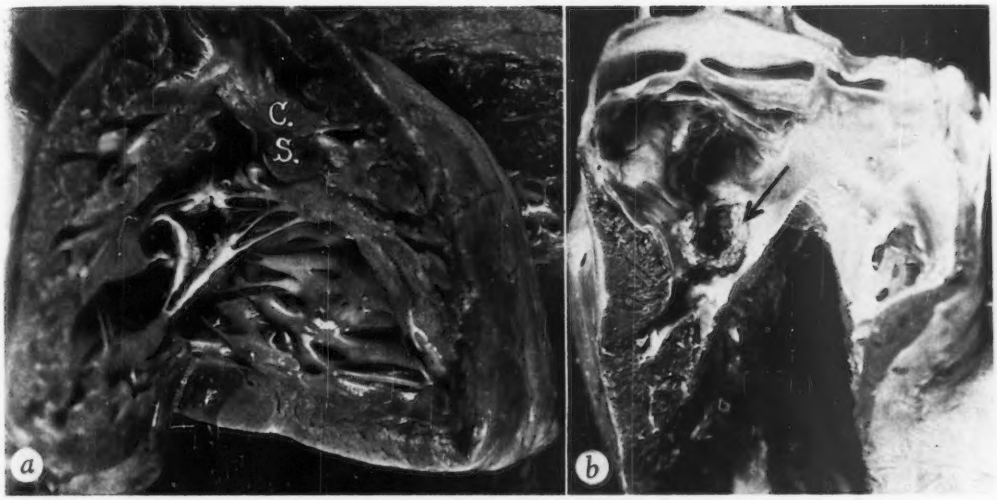

Figure 5

Case 1. a. *Right ventricle. The outflow tract of the right ventricle is divided by a prominent crista supraventricularis (C.S.), anterior to which is a stenotic infundibular tract leading to the pulmonary trunk, which is guarded by a bicuspid valve. Posterior to the crista supraventricularis lie the subaortic tract and the large ventricular septal defect. In this view, the tricuspid valve is seen from below and is unopened. Vegetations of healed bacterial endocarditis appear on the atrial edges of the valve.* b. *The infundibular subpulmonary chamber and pulmonary valve. The arrows point to the lower ostium of the infundibular chamber, which is stenotic and about which vegetations of healed bacterial endocarditis are present.*

cuspid and stenotic. The aorta arose from both ventricles above the ventricular septal defect.

Up to this point, the description of this heart is that of the classic anatomic tetralogy of Fallot. However, an additional malformation related to the tricuspid valve was present that evidently had modified the functional state from that in the usual tetralogy of Fallot. The tricuspid valve possessed the usual 3 leaflets but, in addition, an accessory flap extended from the ventricular aspect of the tricuspid annulus into the right ventricular cavity (fig. 6*a*). The lower edge of the accessory flap received a set of chordae that inserted into the papillary muscle of the conus of the right ventricle. The upper edge of the flap was attached to the lower end of the ventricular septal defect. The long axis of the accessory flap was parallel to the long axis of the ventricular septal defect. An attempt was made to simulate the effect of ventricular systole on this anomalous flap. When pressure was exerted against the lower aspect of the flap, it was possible to have it engage and almost close the ventricular septal defect (fig. 6*b*).

An additional remnant of accessory valvular tissue extended upward from the upper edge of the ventricular septal defect to the right ventricular wall. The posterior leaflet of the tricuspid valve revealed an accessory orifice about which chordae were inserted (fig. 7*a*).

In addition to the afore-mentioned changes, both the tricuspid valve and the upper edges of the stenotic zone in the subpulmonary tract showed partly calcified vegetations that histologically were consistent with the appearance of healed bacterial endocarditis.

The left ventricular cavity contained a mural thrombus undergoing organization at its apical portion (fig. 7*b*). This lesion was interpreted as the site of healed mural endocarditis.

The aortic arch was anomalous. The arch passed over the right main bronchus, and the descending aorta lay to the right of the esophagus in its greater course through the thorax. In the lower portion of the thorax, the aorta deviated to the left and entered the abdomen through a normally positioned aortic hiatus of the diaphragm.

The branches of the aortic arch were mirror images of the normal. The following branches arose from before backward: the left innominate artery, the right common carotid artery, and the right subclavian artery. The left innominate ar-

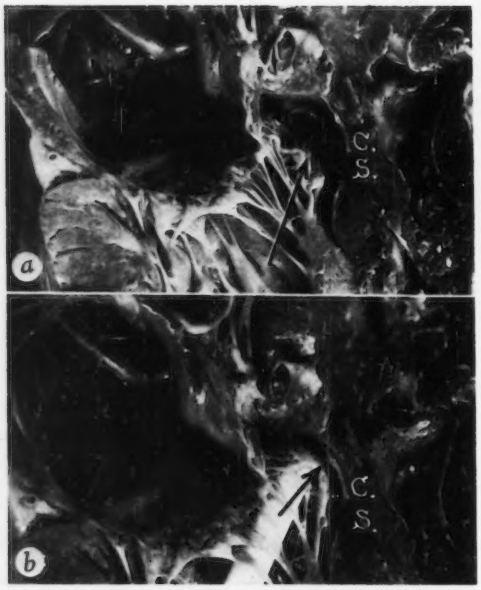

Figure 6

Case 1. a. *Outflow tract of right ventricle and tricuspid valve. Behind the crista supraventricularis (C.S.) is a large ventricular septal defect. The arrow points to an accessory flap of tissue attached to the ventricular aspect of the tricuspid valve. In this view, the flap is in a simulated diastolic position.* b. *Same specimen. A probe has been placed under the accessory flap of the tricuspid valve (arrow) and pushed upward, simulating the effect of systole on the accessory flap. This simulated systolic position of the flap shows that the ventricular septal defect is all but closed by the flap when it is pressed into the defect.*

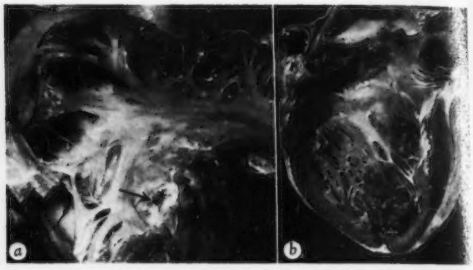

Figure 7

Case 1. a. *Right atrium and tricuspid valve. The posterior leaflet of the tricuspid valve has an accessory congenital orifice (point of arrow). The valve of the inferior vena cava is represented by a network of delicate fibrous strands. Inferior to the orifice of the inferior vena cava, the orifice of the coronary sinus is closed. Vegetations of bacterial endocarditis are seen on the atrial aspect of the tricuspid valve.* b. *Left ventricle and aortic valve. Inferior to the aortic valve is a large ventricular septal defect. The aorta straddles the defect. An organizing mural thrombus is present in the apical portion of the left ventricle.*

tery was long, and a segment was present between the origin of the left common carotid and left subclavian arteries that showed an infolding of the superior aspect like that seen in coarctation of the aorta. The ligamentum arteriosum was left-sided and extended from the left pulmonary artery to the left innominate artery, inserting opposite the origin of the left subclavian artery.

Study of the interior of the right atrium showed that the orifices of the superior and inferior venae cavae were in normal positions. The foramen ovale was closed. The right atrial ostium of the coronary sinus was closed by a delicate flap, presumably representing adhesion of the valve of the coronary sinus to the right atrial wall. The only recognized outlet for coronary venous blood was a series of dilated thebesian veins in the left atrium. A persistent left superior vena cava was not present; such an absence also is noted in other cases of atresia of the right atrial ostium of the coronary sinus.[1]

Cases 2 and 3. In these 2 cases, operations were performed after necropsy had been done in the first case. The basic malformation, as identified by the surgeon, in cases 2 and 3 was the tetralogy of Fallot, including the presence of a large ventricular septal defect. In each instance, an accessory flap of tissue also lay inferior to the tricuspid valve and in close relationship to the ventricular septal defect. The flap in each case was in such a position and of such nature that it was considered possible that it had been able to close the ventricular septal defect partially during ventricular systole.

Discussion

Although the wide functional range represented by the tetralogy of Fallot is now well known,[1, 10, 11] the 3 cases reported here must be considered as a special group from pathologic and hemodynamic points of view.

The patients presented a general clinical picture of severe obstruction to outflow from the right ventricle, associated with cyanosis. The clinical history did not aid in the differential diagnosis. The physical findings were most suggestive of severe pulmonic stenosis with an intact septum. A forceful impulse of

the right ventricle is unusual in the tetralogy of Fallot, but it was observed in 2 of these 3 patients. Distended cervical veins as a clinical sign of increased right atrial pressure are unusual in the tetralogy of Fallot but are often seen in severe pulmonary stenosis with an intact ventricular septum.

Congestive right heart failure is extremely unusual in the tetralogy of Fallot; it was present in 1 of our cases.

The electrocardiogram showed pronounced right ventricular hypertrophy in all cases, especially case 2, in which the deep, sharply inverted T waves in leads from the right side of the precordium suggested that the right ventricular pressure was greater than the systemic pressure.

The radiologic findings of cardiac enlargement in cases 1 and 2 were also unusual for the tetralogy of Fallot, although the presence of a right aortic arch in case 1 was more in favor of this anomaly than it was of pulmonary stenosis with an intact ventricular septum.[6]

The findings at cardiac catheterization, as already mentioned, showed a significantly higher systolic pressure in the right ventricle than in the systemic circulation. Since it is usually assumed that the right ventricular pressure in the tetralogy of Fallot is about equal to the systemic pressure,[6, 8] finding of a significant differential immediately places doubt on the diagnosis of a classic tetralogy.

We think that the additional flap on the tricuspid valve was responsible for the increase of right ventricular pressure, as this flap partially closed the ventricular septal defect during systole. This partial closure of a large defect during ventricular systole changes the dynamics from those of the usual tetralogy of Fallot into those representative of cases with severe pulmonary stenosis and a small ventricular septal defect.

The clinical entity of pulmonary stenosis with an anatomically small ventricular septal defect apparently is extremely rare.[1, 11, 12] In reported cases of such an anomaly, the hemodynamic and clinical data have been similar to those seen in the present 3 cases.

Summary

An anatomicopathologic entity of the tetralogy of Fallot with an additional finding of an accessory flap of tricuspid valvular tissue is described. In the 3 cases reported in this paper, the outstanding hemodynamic finding was a right ventricular systolic pressure that was significantly greater than the systemic systolic pressure.

The hemodynamic findings were explained by the fact that the accessory tricuspid flap partially closed the large ventricular septal defect.

The clinical picture was similar to that of either severe pulmonary stenosis with an intact ventricular septum or severe pulmonary stenosis with a small ventricular septal defect and a right-to-left shunt at the ventricular level.

Summario in Interlingua

Es describite un entitate anatomico-pathologic de tetralogia de Fallot con le constatation additional de un lobo accessori de tissu de valvula tricuspidal. In le 3 casos reportate in le presente communication, le plus frappante observation hemodynamic esseva un tension systolic dextero-ventricular significativemente plus grande que le systemic tension systolic.

Le characteristicas hemodynamic se explicava per le facto que le lobo accessori tricuspidal claudeva partialmente le grande defecto ventriculo-septal.

Le tableau clinic esseva simile a illo de (1) sever stenosis pulmonar con intacte septo ventricular o (2) sever stenosis pulmonar con un micre defecto ventriculo-septal e un shunting dextero-sinistre al nivello ventricular.

References

1. EDWARDS, J. E.: Congenital malformations of the heart and great vessels. *In* Gould, S. E.: Pathology of the Heart. Ed. 2. Springfield, Ill. Charles C Thomas, 1959, p. 260.
2. BAFFES, T. G., JOHNSON, F. R., POTTS, W. J., AND GIBSON, S.: Anatomic variations in tetralogy of Fallot. Am. Heart J. 46: 657, 1953.
3. BRINTON, W. D., AND CAMPBELL, M.: Necropsies in some congenital diseases of the heart, mainly Fallot's tetralogy. Brit. Heart J. 15: 335, 1953.
4. EDWARDS, J. E., BULBULIAN, A. H., AND ROGERS, H. M.: Pathologic and embryologic considerations in tetralogy of Fallot. Proc. Staff Meet., Mayo Clin. 22: 166, 1947.
5. KJELLBERG, S. R., MANNHEIMER, E., RUDHE, U., AND JONSSON, B.: Diagnosis of Congenital Heart Disease. Chicago, The Year Book Publishers, Inc., 1955, 649 pp.
6. KEITH, J. D., ROWE, R. D., AND VLAD, P.: Heart

Disease in Infancy and Childhood. New York, The Macmillan Company, 1958, 877 pp.

7. EDWARDS, J. E., DRY, T. J., PARKER, R. L., BURCHELL, H. B., WOOD, E. H., AND BULBULIAN, A. H.: An Atlas of Congenital Anomalies of the Heart and Great Vessels. Springfield, Ill., Charles C Thomas, 1954, 202 pp.
8. BLOUNT, S. G., JR.: Congenital heart disease—cyanotic. *In* Zimmerman, H. A.: Intra Vascular Catheterization. Springfield, Ill., Charles C Thomas, 1959, p. 264.
9. BING, R. J., VANDAM, L. D., AND GRAY, F. D., JR.: Physiological studies in congenital heart disease. II. Results of preoperative studies in patients with tetralogy of Fallot. Bull. Johns Hopkins Hosp. 80: 121, 1947.
10. BURCHELL, H. B.: Basis of cyanosis in tetralogy of Fallot. Proc. Staff Meet., Mayo Clin. 22: 162, 1947.
11. McCORD, M. C., VAN ELK, J., AND BLOUNT, S. G., JR.: Tetralogy of Fallot: Clinical and hemodynamic spectrum of combined pulmonary stenosis and ventricular septal defect. Circulation 16: 736, 1957.
12. McGOON, D. C., AND KIRKLIN, J. W.: Pulmonic stenosis with intact ventricular septum: Treatment utilizing extracorporeal circulation. Circulation 17: 180, 1958.

We may say on the grounds of incontestible experience, that, in their early stages, they are, in a large proportion of instances, susceptible of a perfect cure; and that, when not, they may, in general, be so far counteracted as not materially, and sometimes not at all, to curtail the existence of the patient. We may, accordingly, predict that the term "disease of the heart," which at present sounds like a death-knell when uttered by the physician, will hereafter become by familiarity not more alarming than the term *asthma*, under which it is frequently disguised.—J. HOPE, M.D. *Diseases of the Heart and Great Vessels.* London, William Kidd, 1832, p. 20.

Serum Cholesterol and Relative Body Weight of Coronary Patients in Different Populations

By ANCEL KEYS, PH.D., AND FLAMINIO FIDANZA, M.D.

COMPARISONS of coronary patients with their clinically healthy counterparts in areas where coronary heart disease is extremely common show that the patients tend to have serum total cholesterol concentrations higher than the "controls."[1-10] Prospective studies in the United States show that this tendency exists before the disease is clinically apparent.[10-15]

Similarly, populations that apparently differ in the frequency of coronary heart disease show corresponding differences in the average serum cholesterol values of men of given age in those populations.[11-28]

These facts and other evidence lead to the hypothesis that the serum cholesterol concentration is an important causal factor in the development of atherosclerosis and its complications in the form of clinical coronary heart disease. Not unnaturally, this view is sometimes interpreted to mean that the disease is a result of a "metabolic fault" that produces cholesterol levels above some critical level at which atherosclerosis is promoted. In turn, the objection is raised that many coronary patients are reported to have cholesterol levels that are not particularly high in comparison with the general population or presumed "norm" for the U.S. But there is very little information on coronary patients in populations in which the disease is less common than here.

While most investigators now accept the view that serum cholesterol does play a role in the etiology of coronary heart disease, there seems to be even wider acceptance of the view that overweight is contributory. The prospective studies mentioned above indicate that overweight has much the same predictive value for future clinical disease as does the cholesterol level; perhaps more influential is the evidence from the insurance industry that the risk of future mortality among insured policy holders is increased with increasing levels of relative body weight at the time of the insurance examination.[29-31] We have pointed out some of the weaknesses of the conclusions from these insurance data[32-34] but the massive numbers of policy holders involved are impressive and undoubtedly justify actuarial conclusions about the risk of mortality of insurance applicants.

Naturally, therefore, there is great interest in obtaining data on "normal" values of serum cholesterol and relative body weights and on these characteristics in coronary patients, particularly since both of these characteristics are readily modified by the diet. These efforts so far have been largely confined to the analysis of data from the United States and a few similar "high coronary" populations. But it is instructive to inquire into the characteristics of men with coronary heart disease, compared with suitable controls, in other populations as well as in the United States. The present paper reports findings in Naples, Italy, and in the Twin Cities of Minneapolis and St. Paul, Minnesota.

Subjects and Methods

Coronary Patients

Any study in the United States on serum lipids and overweight in coronary patients is currently apt to be seriously complicated by the increasing tendency of physicians to prescribe, and the patients themselves to adopt, dietary or pharmaceutical programs to reduce the blood cholesterol level or the body weight or both. During the past

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Aided by research grants from the American Heart Association, New York, the U. S. Public Health Service (grant recommended by the Cardiovascular Study Section), the Winton Companies Fund and Mr. David Winton, Minneapolis, Minn.

few years more than half of the coronary patients from the Twin Cities seen in the Laboratory of Physiological Hygiene have made some dietary change before we saw them. Accordingly, for the present analysis we have elected to concentrate on coronary patients studied in the years 1953 to 1955, at which time our methods were standardized in the present form but deliberate attempts to control blood cholesterol and body weight in coronary patients were much less common than now. A secondary series of patients studied in 1955 to 1957 will be noted also.

In Naples, Italy, relatively little emphasis has been given until very recently to cholesterol and weight control of coronary patients, and dietary alterations after the appearance of the clinical disease did not appreciably affect the series in the years 1957 to 1959, which are reported here.

The upper age limit of 65 years was set for the coronary patients and all but 4 of the total of 218 patients thus included were 40 years old or more, 2 of these men being in the Twin Cities and 2 in Naples.

The Twin Cities coronary patients were urban residents whose occupation was of the white-collar type—business, professional, and clerical—and none had been engaged in manual labor. No special selection was made, however, in regard to social or economic status. They were seen through the cooperation of several local internists who were asked to refer their male coronary patients up to age 65 who could be brought to the Laboratory of Physiological Hygiene for examination. They were asked not to refer patients because of known abnormality of lipid metabolism and to exclude patients in whom the coexistence of disease besides coronary heart disease might be a complicating factor. Further, they were requested not to refer patients for whom they had already prescribed dietetic or medication programs designed to control blood cholesterol or body weight.

These stipulations were adhered to in general, but several patients had to be excluded when we discovered exceptions. Several other patients were excluded because they were not clearly cases of coronary heart disease.

The medical criterion for inclusion in the Twin Cities coronary series was clear evidence of previous myocardial infarction or of classical Heberden's angina pectoris. Almost all the patients in the latter category exhibited one or another electrocardiographic abnormality, depressed S-T segments and T waves if not QRS indications of old infarction.

The Neapolitan coronary patients were seen through the cooperation of Dr. Mario Mattioli and the internists in charge of cardiovascular patients in the University Clinics. Only patients with clear evidence of previous myocardial infarction were included. Because myocardial infarction in the general poor population of Naples is apparently much less common than among the wealthy class there or than in Minnesota, special efforts were made to seek out patients in the working classes. For this and other reasons, the social class distribution of coronary patients studied in Naples may not be representative of the true distribution of infarction by socioeconomic class in that city.

Control Subjects

In order to match the age range of the coronary patients the men to be considered as control subjects were restricted to ages 40 to 66. They were all fully employed at the time of study and were judged to be clinically healthy on the basis of medical examinations.

The Twin Cities control subjects were men engaged in professional, business, or clerical work in the Twin Cities, none was engaged in manual labor, and they were considered to correspond reasonably closely to the coronary patients in social and economic status. Both control and coronary series included some business executives, physicians, and wealthy men and, in general, were probably more representative of the upper class of the Twin Cities than of the general population.

The Twin Cities control subjects were almost all secured by invitation of men whose names were on rosters of employees supplied by 28 corporations in Minneapolis and St. Paul. About 90 per cent of the invitations were accepted. In addition to those on these rosters, about 10 per cent of the Twin Cities control subjects were self-employed or employees of firms other than the major list of corporations who had learned of our program from friends on the roster and were included at their request after we were convinced they were not simply hypochondriac or otherwise peculiar.

In Naples it was considered essential to secure control subjects in several socioeconomic classes. There is a major difference between the upper class of business and professional men and the general population of the working class whose mode of life is greatly different in several respects, notably in the diet. Further, within the general working class distinction should be made between clerical workers and other relatively sedentary men of the poor class on the one hand and men doing heavy manual work on the other, even though in Naples there is little difference in economic status between these types.

Accordingly, business and professional men were recruited through the Rotary Club of Naples and through professional colleagues. Several cases of coronary heart disease were found in this group (and were included in the coronary series), and the remainder are considered as "controls." Cler-

ca' workers were secured through cooperation of tl City and State Tax Offices of Naples. Most o the men accepted the opportunity of examinati n, without deduction of pay for time off the jo .

Physically active workers in Naples were repr ented by 3 groups of men. Workers of one sh ift at one section of the Ilva steel mills were e amined on the premises and, because of conv nience and no loss of pay for time off, few d clined. The second group consisted of regular m embers of the City Fire Brigade stationed at t eir main station and headquarters a few yards f om the Institute of Physiology. Over 90 per c nt of the firemen of acceptable age accepted the examination. Finally, a group of stevedores from the municipal international dock were examined and, again, most of those given the opportunity agreed to the examination.

Technic

Venous blood samples were drawn in the resting state without stasis and total cholesterol was measured in the serum by our modification[35] of the method of Abell et al.[36] In many samples total cholesterol was also measured in the alpha- and beta-liprotein fractions as separated by paper electrophoresis.[35] All analyses were performed in duplicate. Identical methods were used in Minneapolis and in Naples and strict comparability of results in the two cities was assured by many exchanges of materials for analyses as well as exchanges of scientific personnel between the two laboratories.

Relative body weight was calculated from the recorded (nude) weight and (barefoot) height, by the use of standard tables for "average" weight at given height and age.[29] We hold no brief for these tables as indicators of either the actual or the desirable body weight of the U. S. or any other population,[32-34] but they do provide a generally available reference system in which individuals of differing height and age can be compared in terms of a single variable of relative weight.

Variability of Serum Cholesterol

All values reported here are subject to 2 sources of variation other than the variability among individuals. The first source, the error of the analytical measurement, is small, as shown by many series of replicate analyses. Elsewhere,[17] we have reported a value of ± 3.64 mg. per 100 ml. for the standard error of measurement in 1,668 pairs of duplicate analyses using the present method in our Minnesota laboratory, the compution being $(SEM)^2 = (\Sigma\Delta^2)/2N$, in which Δ is the difference between duplicates and N is the number of pairs. Almost identical values for SEM were obtained in several series analyzed in the Naples laboratory. Recently our Minnesota laboratory participated in a cooperative study of variability of cholesterol measurement supervised by the Communicable Disease Center of the U. S. Public Health Service, duplicate serum samples being received in different batches for analysis blind. From the report from the statistical office of the Center we find that for analyses reported from our Minnesota laboratory the value was SEM = ±5.0, the slightly higher value than noted above being accounted for perhaps by the fact that in this test the duplicates were analyzed on different days and involved various technicians and equipment. In actual practice here the value of SEM is smaller than ±5.0 because, after the analyses of the duplicates are recorded, when any pair differs by as much as 20 mg. per 100 ml., the analyses are repeated on serum saved for the purpose.

The present study is based on the means of duplicate analyses in all cases so the error of analytical measurement, taken as the repeatability of the means of duplicates, must have been less than the values of SEM cited above and may be estimated as between 2.6 and 3.6 mg. per 100 ml. As will be seen below, this source of variability accounts for only a small fraction of the total intra-individual variability observed in the present study.

Analytical error in serum cholesterol estimation may be serious in many routine laboratories.[37] But even in that study in which the standard error of measurement in commercial laboratories was many times what should be considered acceptable, it appeared that biologic variation is more important.

Intra-individual variability was estimated from the results of blood samples drawn fom the same individuals on different occasions. Blood samples were drawn twice, at an interval of 2 to 6 weeks, from each of 60 clinically healthy, middle-aged men who were living and working as usual. The grand mean for these men was 244.4 and the standard error of measurement, calculated from the 60 pairs of mean values (or duplicates) was SEM = 18.1.

A special study was done on coronary patients from whom blood samples were drawn at monthly intervals for 4 consecutive months. All these patients suffered from angina pectoris and most of them had had one or more myocardial infarctions but none as recently as 3 months before the start of the study. These patients were under no special dietary control except that they were asked not to make conscious changes in their diets. At monthly interviews they reported that their diets were "about the same." No major changes in clinical status in the 30 patients retained for analysis here were noted during the 4-month period. It was considered that the intra-individual

Table 1

Intra-Individual Variability of Serum Total Cholesterol Concentration in Middle-Aged Men

Group	No.	Mean (mg./100 ml.)	SEM
Healthy controls	60	244.4	18.1
Coronary patients	30	266.0	24.4
Coronary patients, "low"*	15	232.3	16.7
Coronary patients, "high"*	15	299.6	30.1

*Lower and upper halves of the cholesterol distribution.

variability observed in the 4 blood samples in this series should be fairly representative of non-hospitalized male coronary patients aged 40 to 66.

The results from this study are summarized in table 1. With 3 or more replications, $SEM^2 = (T\text{-}T_1)/N(k\text{-}1)$, in which N = number of individuals, k = number of replications, T = sum of the squares of all values on all individuals on all occasions, and T_1 is $1/k$ times the sum of the squared sums of all values for each individual. In order to see whether intra-individual variability is related to the mean cholesterol value of the individual, the 30 patients were divided into halves, the 15 patients with the lower mean cholesterol values and the 15 patients with higher values.

It appears that the more hypercholesteremic patients are much more variable than those with lower mean values, SEM being almost twice as great in the patient with a mean cholesterol value of 299.6 as in those with a mean of 232.3. But the data do not suggest any real difference between the patients and the healthy men other than that associated with the difference in mean cholesterol level. It appears that only from about 2 to 6 per cent of the total variance within individuals may be ascribed to analytical error, the remainder being biologic variability, including that of the diet.

Recent versus Old Myocardial Infarcts

The coronary patients in Naples were comprised of 38 men who had suffered a myocardial infarct within 30 days before examination and 70 men whose infarcts were older. Before a general analysis was attempted of the combined Neapolitan data, these two groups were compared. No significant difference was found between the means for age, relative body weight, or serum cholesterol concentration, the nearest approach to significance being in the last named variable. The mean serum cholesterol value of the men with recent infarcts was 11.4 mg. per 100 ml. higher than in those with old infarcts but the standard error of this difference was ±9.1, and the value of t of only 1.25 indicates that such a difference would be expected to occur by chance in about 1 out of 4 trials. Accordingly, general analysis was undertaken disregarding the age of the infarct.

Results

Coronary versus Control Subjects

The general results are summarized in table 2 with statistical analysis in table 3. Age matching between coronary and control subjects was satisfactory but in regard to both relative body weight and serum cholesterol concentration there were highly significant differences between groups.

In the Twin Cities there was obviously no difference in relative body weight between patients and control subjects and neither group contained a high frequency of overweight men. Among the 72 coronary patients there were only 12 men who were 10 per cent or more above the standard average relative body weight of the Medico-Actuarial tables and only 4 men were as much as 20 per cent overweight according to these criteria. In contrast, all of the Neapolitan groups except the working class control subjects tended to be overweight and within each Naples class the coronary patients tended more often to be overweight than the men in their control group though the latter difference was not significant for the upper class. Among the 54 working class Neapolitan coronary patients only 9 were as much as 10 per cent overweight but these included 5 men over 20 per cent overweight of whom one was a clerk with relative weight 145 who had had an infarct 2 months previously and who was the fattest man in the entire series of 751 men reported here.

The serum cholesterol trend is striking. As expected, both of the Twin Cities groups had significantly higher averages than either of the Neopolitan control series and the coronary patients in the Twin Cities differed from the Twin Cities control subjects with high significance. But even the Twin Cities control subjects had higher values than the Neapolitan coronary patients. Further, in each social class in Naples the patients had higher cholesterol averages than their control subjects. It is obvious that these data do not support the idea that there is a "normal serum choles-

Table 2

Means, and Standard Errors, for Relative Body Weight and Serum Total Cholesterol, in Men Aged Under 65 with Coronary Heart Disease and in Clinically Healthy Men Aged 40 to 65.

Group	No. men	Age	Relative body weight	Total cholesterol mg. %
Twin Cities coronaries	72	52.8	98.7 ± 1.4	258.9 ± 4.1
Twin Cities controls	338	53.2	98.0 ± 0.9	238.9 ± 2.4
Naples upper class coronary patients	54	53.2	107.1 ± 1.4	217.6 ± 6.5
Naples upper class control subjects	89	50.3	104.5 ± 1.7	201.3 ± 5.1
Naples working class coronary patients	54	53.1	103.6 ± 1.5	203.7 ± 5.2
Naples working class control subjects	144	51.4	97.6 ± 1.4	170.7 ± 2.6

Table 3

Statistical Analysis of the Differences between the Several Groups of Patients and Control Subjects

Comparison	Degrees of freedom	Relative weight Δ	Relative weight F	Cholesterol Δ	Cholesterol F
T. W. coronary minus T. W. control	408	0.7	—	20.0	13.06
T. W. coronary minus Naples I coronary	124	−8.4	17.14	41.3	31.40
T. W. coronary minus Naples II coronary	124	−4.9	5.26	55.2	71.66
Naples I coronary minus Naples II coronary	106	3.5	2.71	13.9	2.79
Naples I coronary minus Naples I control	141'	2.6	1.14	16.3	3.87
Naples I control minus Naples II control	231	6.9	8.27	28.7	30.03
T. W. control minus Naples I control	425	6.5	11.07	37.6	49.27
Naples II coronary minus Naples II control	196	6.0	4.88	31.1.	35.12

T. W. = Twin Cities, Naples I and Naples II designate upper and working classes, respectively. The probability values associated with the F values are 3.92, 6,85, and 11.38 for $p = 0.05$, 0.01 and 0.001, respectively, for 120 degrees of freedom (d.f.) and for d. f. $= \infty$ the corresponding F values are 3.84, 6.64, and 10.83.

terol'' level for clinically healthy middle-aged men in general or that there is some kind of a critical level that distinguishes all or average coronary patients.

Analysis of the cholesterol data in terms of frequency distribution rather than mean values shows that the differences between the means are not due to a few extreme values. In the Twin Cities, 56 of 72, or 78 per cent, of the coronary patients had cholesterol values above the control median. Among the Naples coronaries 32 of 54 of the upper class patients were above the median of the upper class control and 44 of the 54 working class patients were above their control median.

The ''working class'' samples in Naples comprise men at the same general socioeconomic level who differed markedly in physical activity, at least prior to infarction. It is of interest, therefore, to compare the clerical workers with the men in occupations involving heavy manual labor as analyzed in table 4. The manual workers do not differ significantly from the clerical workers in relative body weight or in serum total cholesterol but in each of these activity categories the coronary patients tend to be relatively heavier and to have much higher serum cholesterol values than their controls of the same age and activity.

Alpha and Beta-Lipoprotein Cholesterol

In previous reports[18, 19, 38-40] we have shown

Table 4

Relative Body Weight and Serum Total Cholesterol of Coronary Patients and Control Subjects in the Working Class in Naples

Group	No. men	Relative body weight Mean	Relative body weight SE	Cholesterol, Mg. % per 100 ml. Mean	Cholesterol, Mg. % per 100 ml. SE
Manual workers, coronary patients	32	101.1	±1.5	202.3	±6.4
Manual workers, control subjects	109	97.7	±1.5	170.5	±3.0
Clerical workers, coronary patients	22	107.2	±5.2	205.8	±3.0
Clerical workers, control subjects	35	97.0	±2.1	171.3	±6.3

Table 5

Means and Standard Errors for Alpha- and Beta-Lipoprotein Cholesterol Concentrations, mg. per 100 ml. of Serum, in Men Under 65 with Coronary Heart Disease and in Age-Matched Clinically Healthy Control Subjects

Group	No. men	α Cholesterol	β Cholesterol
Twin Cities coronary patients	60	37.4 ± 1.4	221.5
Twin Cities control subjects	332	41.0 ± 0.6	197.9
Naples coronary patients	56	34.4 ± 1.2	179.4
Naples control subjects	60	40.6 ± 1.2	155.0

that the serum total cholesterol differences among clinically healthy populations as well as the changes induced by dietary alterations are entirely accounted for by changes in the cholesterol concentration in the beta-lipoprotein fraction of the serum. Table 5 summarizes the findings on the serum separated into 2 fractions by paper electrophoresis.

The Twin Cities and the Naples Control Subjects differ greatly in beta-lipoprotein cholesterol but they have almost identical mean values for cholesterol in the alpha-lipoprotein fraction. This corresponds with all our previous findings in samples of clinically healthy men. The coronary patients, however, clearly tend to have lower alpha-lipoprotein cholesterol values both in the Twin Cities and in Naples and the averages of these two patient groups are not significantly different from each other. This corresponds with the reports of others that alpha-lipoprotein tends to be diminished in coronary patients.[1, 4, 6, 10, 41] Elsewhere we have reported that alpha-lipoprotein cholesterol concentration in man is stable, in contrast with the beta fraction, in the face of dietary differences, both in controlled experiments[18, 40, 41] and in populations.[18, 19, 40]

Relationship between Relative Weight and Serum Cholesterol

Previously we reported that among clinically healthy men of given age in restricted socioeconomic classes and cultures there is at most only a small correlation between relative obesity, or relative body weight, and serum cholesterol concentration. Table 6 summarizes the examination of this question with the coronary patients studied here. Each group of patients was classified in regard to relative body weight so we have 3 non-overlapping classes with approximately equal numbers of men in each. Table 6 gives the mean values for relative body weight and serum cholesterol for each of these classes.

In both socioeconomic classes in Naples the most underweight patients tend to have substantially lower serum cholesterol values than the rest of the patients in their class but the most overweight patients are no different in serum cholesterol from the patients with medium relative body weight. Among the Twin Cities patients there is no significant differ-

Table 6

Mean Serum Cholesterol Values, mg. per 100 ml., in Coronary Patients Classified According to Relative Body Weight into Nonoverlapping Groups with Mean Relative Body Weights

Patients	Most underweight			Middle weight			Most overweight		
	No.	Relative weight	Cholesterol	No.	Relative weight	Cholesterol	No.	Relative weight	Cholesterol
Naples upper class	18	95.9	202.4	17	106.3	229.3	19	118.3	221.4
Naples working class	19	94.1	188.2	17	101.9	211.6	18	115.2	212.8
Twin Cities	23	86.6	262.7	26	98.2	259.4	23	111.4	254.5

ence in serum cholesterol among the three relative body weight groups.

It is obvious that if socioeconomic class were ignored, various relationships between relative body weight and serum cholesterol might be indicated, depending on the groups and the numbers in them. But such spurious relationships would be accounted for by the characteristics of the groups and not by any necessary real relationship between the 2 variables.

Twin Cities Coronary Patients in 1957 to 1959

During 1957 to 1959 Twin Cities coronary patients, referred by cooperating physicians as in 1953 to 1955, were studied. After omission of patients over 65, those whose referral was related to previous findings of peculiarities in serum cholesterol obtained elsewhere, and those who were following management programs of drugs and diet prescribed by their physicians to control cholesterol, there were 36 business and professional men judged to be comparable to the patients of 1953 to 1955 that are reported in this paper. From interviews it was found that 20 of the 36 men had made significant changes in their diets since diagnosis of the disease. The dietary changes involved reduction in calories or fats or both and had been made because of concern about the possible ill effects of high-fat and high-calorie diets. In most cases it appeared that a decision to make dietary changes stemmed from information from mass media, reinforced by discussions with friends and physicians, the latter, however, not going so far as to prescribe dietary alteration.

The average age of these 36 patients was 54.6 years and their average total cholesterol concentration was 246.5 mg. per 100 ml. of serum, with a standard error of ±8.0. This average is 13.4 mg. per 100 ml. lower than the average for the 1953 to 1955 series but it does not attain statistical significance because of the large variability in the 1957 to 1959 series.

Experience in the Twin Cities more recently (1959 to 1960) continues to show this trend, in which fewer and fewer patients seen a month or more after diagnosis of coronary heart disease are found who have not changed their diets or taken drugs to control the blood cholesterol level. While this may be laudable in many respects, it does mean that it becomes increasingly difficult to obtain valid samples of coronary patients in this region whose cholesterol values may be representative of the natural history of the disease.

Discussion

Intra-Individual Variability

Previously published analyses of variability in serum cholesterol concentration are not strictly comparable with the present material. The 33 men reported by Watkin et al.[42] were elderly hospitalized patients living a monotonous life in a single institution on a diet stated to be "remarkably constant from day to day"; their variability cannot be accepted as representative of nonhospitalized men living "ad lib." Those patients, further, were considerably older (average about 70 years) and their cholesterol levels were much lower (average about 198 mg. per 100 ml.) than the men studied in the Twin Cities. Apparently the intra-individual variability of that group was somewhat lower than in any of the groups reported here in table 1 but would correspond roughly to the present data, if

consideration were given to the trend of variability to rise with the mean cholesterol level.

The study of cholesterol variability made by Thomas and Eisenberg[43] concerned Johns Hopkins medical students who were much younger and had lower cholesterol values than the men in table 1. The Bloor method used by Thomas and Eisenberg was stated to be satisfactorily reproducible but their data on the standard error of measurement of duplicate analyses, computed as in the present paper, indicates an analytical error about twice as large as in our laboratory. The Bloor method used by Thomas and Eisenberg systematically gives values about 15 per cent higher than our method. This difference is caused by the fact that ester cholesterol gives a more intense color with the Lieberman-Burchard reagent than does free cholesterol. Free cholesterol is used as the standard, both in the Bloor and the present method, but in the Bloor method the ester cholesterol in the serum is not hydrolyzed to the free form as is done in our method.

The intra-individual variability observed by Thomas and Eisenberg is greater than found here. For young men studied at intervals of 12 to 18 months, values of SEM (as in our table 1) were 34.7, 27.3 and 37.4 mg. per 100 ml. (Bloor method) for groups with initial cholesterol values of 150 to 199, 200 to 249 and 250 to 299, respectively. In terms of the method used here, these SEM values would correspond to about 30, 23, and 32. In another series average values in units corresponding to our method of SEM = 24, 25, 23, and 24 were obtained for repetitions less than 5, 6, 7, and 12 months apart, respectively.

In men on uncontrolled diets, as in all the groups considered here, spontaneous dietary variations undoubtedly contribute to the intra-individual variability. For comparison with the data in table 1, we have the findings in 834 pairs of blood samples from middle-aged men on rigidly constant diets in an institutional situation where there was no possibility of supplementation or alteration of the individual diets.[38] Each pair consisted of 2 samples drawn 1 to 2 weeks apart from 1 man. The value of SEM, calculated as in table 1, was ±11.52 and the grand mean of the 1,668 samples was 228.2 mg. of cholesterol per 100 ml. In another study with soldiers in the U.S. Army, similarly controlled, the SEM from 38 pairs of blood samples drawn 6 to 10 days apart was ±12.0 and the grand mean of the 76 samples was 209.7 mg. per 100 ml.[38] The difference between these values and those in table 1 may be ascribed, at least in part, to the control of the diet and perhaps other stabilizing factors in a situation in which individual freedom is curtailed.

We conclude that something like half of the intra-individual variation observed in men in a stable state of physical health but living under ad lib. conditions possibly may be explained by variations in diet and associated circumstances. But the remaining variability is not explicable from this cause. Some investigators suggest that variations in emotion and stress are influential.[44-47] In none of those studies, however, was there any real dietary control. Whatever may be the cause of this variability, allowance for it must be made in analyzing and interpreting data on serum cholesterol.

Intra-Individual Variability and Group Differences

These data on intra-individual variability provide a basis for estimating the effect of intra-individual variability in masking the real differences among groups of men. This is more easily seen in the hypothetical case in which we have a group of men whose individual true mean cholesterol values, which would be found by many repeated blood samplings, were all exactly the same. We now compare these men with another group, equally homogeneous but with a different common mean cholesterol value. Let us say the first group are coronary patients and their mean is 260 and the second are "healthy control subjects," with a mean of 240 mg. per 100 ml. For simplicity's sake, assume the same intra-individual variability in each group, represented by a value of SEM = 20, as in table 1.

In other words, the true mean value for the serum cholesterol concentration in each

man in the patient group is 260, but if many blood samples were taken from any one patient, the distribution of cholesterol values of these samples would show them spread out around the mean of 260 so that about two thirds of the values would be between 240 and 280, one sixth below 240, and one sixth above 280. The distribution of the values in single samples from all of the patients would be the same, since each sample is presumably a random sample from the patient concerned. The distribution would be the same for the healthy control subjects except it would center on the mean of 240, and two thirds of the values would fall within the range of 220 to 260.

If we have equal numbers, say 50, in each of the 2 hypothetical groups we expect from single blood samples from each man to find the means of the groups to be approximately 260 and 240 and the grand mean to be close to 250. With standard deviations of 20, the expected standard errors of the 2 group means would be about $20/\sqrt{50} = \pm 2.8$ and that of the difference between the 2 group means would be about ± 4. Hence we would have $t = 20/4 = 5$ which indicates a highly significant difference between the 2 groups.

This is very satisfactory but suppose we ask the question, how sharply will a cutting point of 250 separate the 2 groups when each man is represented by a single blood sample? The value 250 as a cutting point is $(260\text{-}250)/20 = 0.5$ standard deviation units below the mean of the coronary patients and an equal amount above the control mean. From tables of functions of the normal probability curve this value of SD = 0.5 indicates that 38 per cent of values for the patient group will be included in the range 250 to 270, while 62 per cent of the values will fall outside these limits, half being on the low side, half on the high side. Accordingly, 31 per cent, or 15 to 16 patients will be expected to be recorded as being *below* the cutting point and an equal number of control subjects will be recorded as *above* this point. In other words, about 31 of the 100 men will have overlapping values in single samples and will be misclassified as to true cholesterol level even though the true mean value of every man in the patient group is 20 mg. per cent higher than the true mean of every man in the control group.

Critics of the hypothesis that serum cholesterol concentration is important in the development of atherosclerosis like to emphasize the observed overlapping between the frequency distributions of cholesterol values in coronary patients and in clinically healthy controls. Being "clinically healthy" at a given examination, however, is far from a guarantee of freedom from serious atherosclerotic development; further, the factors responsible for atherosclerotic development may have ceased to operate long before the clinical situation, perhaps triggered by other unrelated factors, is notable. But aside from these serious complications, the masking effect of intra-individual variability, noted above, must be great. Actually, the values cited above relate only to relatively short-time variability; they must be considered as underestimates of variability over a period of years.

Cholesterol Values—Coronary versus Control Subjects

In view of the evidence presented here in a comparison of relative body weights and serum cholesterol values of coronary patients in different populations, or in different socioeconomic classes, it must be ascertained that the "controls" actually correspond to the patients in all relevant variables save that of coronary disease. An illustration of the difference between matched controls and "controls" without properly matching occupation, etc., is seen in the study of Gertler, Garn, and Lerman[2] on young (under 40) coronary patients. The mean serum cholesterol value of the patients was 286.5 ± 6.6 and that of the matched "controls" was 241.9 ± 5.5. The mean for the less carefully selected "controls" was 224.4 ± 3.5. The literature is replete with examples of the neglect in this regard. It is not acceptable to compare patients and controls who differ in socioeconomic status or in which "controls" are patients "without evidence of disease considered important in cholesterol metabolism."

Table 7

Summary of Comparisons of Men with Coronary Heart Disease with Probably Acceptable Controls in the Same Population

Reference	Age	Control subjects N	Control subjects Cholesterol	Coronary patients N	Coronary patients Cholesterol	Δ Mean
Gertler, Garn, Lerman,[2]	40	97	242	97	287	45
Doyle et al.[13]	39-55	40	244	48	273	29
Lawry et al.[8]	40-49	686	240	70	275	35
Lawry et al.[8]	50-59	357	244	101	262	18
Lawry et al.[8]	60-69	117	235	66	255	20
Epstein et al.[40]: Italo-American	40	215	221	17	235	14
Epstein et al.[40]: Jewish-American	40	311	238	61	241	3
Nikkilä;[4] Keys et al.[52] (Helsinki)	40-62	158	265	26	281	16
Present, Twin Cities	40-65*	338	239	72	259	20
Present, Naples upper class	40-65	89	201	54	218	17
Present, Naples working class	40-65*	144	171	54	204	33

N, number of men; Cholesterol, serum total cholesterol mean, mg. per 100 ml. Ages matched except in the data from Epstein, Simpson, and Boas in which the mean age of coronary patients vs. control subjects was 59 vs. 56 for Italian men and 62 vs. 58 for Jewish men.

*Coronary patients include 2 men under 40 in each of these series.

Table 7 summarizes data comparing coronary patients with clinically healthy men who may be reasonably considered as controls, i.e., actually from the same population and corresponding, in general, in regard to socioeconomic status, etc. But none of the older series is free from cavil.

Some question may be raised in regard to the series reported by Lawry et al.[8] which comprised men, largely self-selected, from many parts of the United States and who do not seem to have been deliberately matched in respect to region, occupation, etc. Though there is no proof of strict comparability in these regards, neither is there any evidence of bias. The series of Doyle et al.[13-15] is confined to State of New York employees in one region but again it is not clear that the various kinds of occupation and socioeconomic status are equally represented in the coronary and the control series.

The series of Epstein et al.[48] is not open to question on these points; all were garment workers in New York City and the 2 groups were clearly distinguished in regard to ethnic origin. But these garment workers were largely in an older age range in which it is generally believed that the relationship of serum cholesterol level to the appearance of the clinical disease is less important than at younger years. Further, the coronary patients, especially the Jewish men, were older than their controls: 42 of 61 of the Jewish coronary patients were over 60 and 10 were over 70, and this proportion of old men was not represented among the control subjects. It should be noted that at ages over 60 the serum cholesterol level tends to fall, at least in clinically healthy men.[11, 49, 52] It is probable that the exclusion of the aged coronary patients from the series of Epstein et al.[48] would result in a larger difference between coronary and control subjects.

In some investigations comparisons between coronary patients and control subjects have been published in a form that does not allow proper summary in table 7. The general nature of the findings in these is at least roughly in harmony with those summarized in table 7. In the Cooperative Study,[11] among the 57 men who subsequently developed coronary heart disease 41 (= 72 per cent) had serum cholesterol values above the median for the population studied, the mean difference between those who did and those who did not subsequently exhibit the disease ranging from

3.4 to 35.5 mg. of total cholesterol per 100 ml. of serum in the 5 subgroups, the grand average difference being 17.4. The 4-year follow-up of 898 men aged 45 to 63 in Framingham, Massachusetts, showed that the 52 new cases of coronary heart disease were distributed so that the new disease rate per 1,000 was 122 among men with serum cholesterol values of 260 or more on the initial examination, 45 among men with values of 225 to 259, and 40 among men with lower initial cholesterol values.[12] In the study of Forssman and Lindegård[13] of 51 coronary patients and 51 pair-matched control subjects the patients had the higher cholesterol values in 34 out of 51 pairs. Further, with 300 mg. of cholesterol per 100 ml. as the point of demarcation, 17 of the 51 patients but only 6 of the 51 control subjects were classed as having "hypercholesteremia."

In South Wales a prevalence study in the population in 2 selected regions included cholesterol measurements on 69 men judged to have "ischemic heart disease" and 205 others (control subjects), the diagnostic label being attached, apparently, on the basis of rather slight indications in most cases, judging from the very high prevalence rate reported.[51] Details were not reported but it was stated that "the (cholesterol) difference (11 ± 14.6 mg. per 100 ml.) between those with and those without ischemic heart disease is small and statistically insignificant." From the standard error reported it would appear that these Welshmen must have been remarkably variable in regard to blood cholesterol. The average age of the coronary subjects, if they may be so termed, was about 60, i.e., somewhat older than the men of our primary concern here.

There are many other series that, unfortunately, cannot be included in table 7 because of lack of information or serious doubts about the control subjects. The series of Barr et al.[1] provides only 21 control men aged 45 to 66, and these do not appear to have been matched to the coronary population in other respects. The several series of Oliver and Boyd[3, 6] provide age and sex matching of control and coronary subjects but the control subjects were made up of various noncoronary patients, medical doctors, etc., who scarcely represent the population from which the coronary patients were drawn. Nevertheless, these and other similar studies with questionable control groups agree in showing that coronary patients do tend to have relatively elevated serum cholesterol levels, especially at younger ages.

Relative Body Weight—Coronary versus Control Subjects

The situation in regard to relative body weight and obesity is equally complicated by failure to assure proper comparability in other respects of control subjects and patients. Because of variations in the methods of evaluating or reporting relative body weight or obesity, the findings in major papers are summarized in qualitative terms only in table 8. In 11 series in which the relative weight status of the patients was ascertained at the time of diagnosis or examination, the patients were not significantly more often overweight than their control subjects in 7 series involving 498 patients, but were more overweight in 4 series involving 237 patients. In 7 series in which evaluation of relative weight was based on data before the appearance of the disease, the patients were not more often overweight in 3 series, involving 968 patients and were more often overweight in 4 series involving 232 patients.

No clear trend emerges from these several studies except the conclusion that the frequency of gross overweight or obesity among coronary patients is not so high as is often thought. In some of the series in which relative overweight of the patients was evaluated at the time of examination or diagnosis it is possible that the finding of overweight underestimated the situation before the disease was first recognized because the patients may have reduced recently. This was not a prominent factor in the Twin Cities and Naples series reported here. On the other hand, in at least some of the series in which the coronary patients significantly tended to be more often overweight than their control subjects, it is

Table 8

Relative Body Weight of Coronary Patients Compared with Their Control Subjects

Authors	No.	When seen	Patients more often overweight
Yater et al.[53]	866	Pre-disease	No
Master et al.[54]			
Anginia pectoris	100	Patients	Yes
Coronary occlusion	100	Patients	No
Coronary occlusion	100	Pre-disease	Yes, recollection
Gertler, White and Others[5]	97	Patients	No
Dawber et al.[12]	52	Pre-disease	Yes
Doyle et al.[15]	57	Pre-disease	Yes
Chapman et al.[55]			
Ages 40-54	13	Pre-disease	Yes
Ages 55-70	24	Pre-disease	No
Epstein et al.[48]			
Italo-Americans	17	Patients	Yes
Jewish-Americans	61	Patients	No
Drake et al.[56]	60	Patients	No*
Forssman and Lindegård[50]	51	Patients	Yes
Buechley et al.[57]	78	Pre-disease	No
Thomas et al.[51]	69	Patients	Yes
Present, Twin Cities	72	Patients	No
Present, Naples upper class	54	Patients	? Not significant
Present, Naples working class	54	Patients	Yes

The column "When seen" indicates whether relative weight was measured as patients or from data some years before clinical disease ("pre-disease").

*Preliminary, from raw data.

not clear that the coronary and control groups were actually matched in regard to occupation and socioeconomic status. The same question can be raised about the studies of the mortality experience of life insurance policy holders.[29-31]

Comment

It is obvious that at present it is increasingly difficult to find coronary heart disease patients after infarction in the Twin Cities who have not embarked on one or another regimen of diet and drugs in an effort to control serum cholesterol or body weight or, more frequently, both. This complication is beginning to appear also in Italy but the natural history of the disease at least in the Naples area is still infrequently masked from this cause. In other parts of the United States too it may be that patients usually suffer their disease without tampering with their diets but it appears probable that the time is coming when it will be difficult everywhere to find relatively young coronary patients, recovered from the acute phase after infarction, whose blood picture represents the situation in which the disease developed. During the acute phase the picture may be misleading. Dodds and Mills[10] report that in many cases cholesterol metabolism is distorted in the acute phase after an infarction. The time may come when the only sure way to discover the long-time characteristics of coronary patients in regard to lipid metabolism will be from long-time prospective studies started when the men in the samples were clinically healthy.

We have no good data on the true frequency of coronary heart disease in any of the populations reported here but from all sources of evidence, including experience of a variety of surveys, hospital populations, etc., it seems clear that there is a marked difference between the Twin Cities and the 2 Neapolitan populations, the frequency of coronary heart disease at less than very advanced ages being most common in the Twin Cities and least common in the Naples working class, the Naples upper class being intermediate. Qualitatively, at least, the serum cholesterol averages seem to correspond with the population frequency of the disease.

In each population the coronary patients tend to be drawn from the upper range of the distribution of cholesterol values in *that* population. But there is certainly no sign of a general critical level for the appearance of the disease. We may theorize that increasing levels of serum cholesterol are associated with increasing risk of the disease though other factors are contributory, perhaps to a major degree. If we have, then, populations with cholesterol frequency distributions differing as to means or other measures of the central tendency, we shall expect to find correspondingly different frequencies of the disease and average levels of serum cholesterol in the coronaries that also differ and are related to the characteristics of the populations in which they occur. This seems to be the situation with the 3 populations in the present study.

Relative body weight appears to play a less important role from these and other data but in some situations relative body weight and serum cholesterol are, or appear to be, interrelated. This interrelationship is most prominent when the population is heterogeneous and embraces large differences in socioeconomic status.

Summary

Men under 66 years of age suffering from unequivocal coronary heart disease in the Twin Cities of Minnesota and in Naples, Italy, were compared with clinically healthy men matched in place of residence, age, type of occupation, and socioeconomic status.

The Twin Cities patients ($N = 72$) did not differ in relative body weight from their controls ($N = 338$) and the average relative weight of both groups was less than either of the 2 Naples coronary groups and the upper class Naples control subjects. The average relative body weight of the upper class Naples coronary patients ($N = 54$) was insignificantly greater than that of their controls ($N = 89$). The Naples working class coronary patients ($N = 54$) had a significant tendency to be more often overweight than their controls ($N = 144$).

The serum total cholesterol concentration was significantly higher in each of the 3 groups of coronary patients than in their corresponding controls and the 3 groups, control and coronary, formed a sharp progression from high to low cholesterol values in the order: Twin Cities, Naples upper class, Naples working class. In the Naples working class, separation into manual and sedentary workers disclosed no differences in either relative body weight or serum cholesterol.

The differences in serum cholesterol were accounted for by cholesterol in beta-lipoprotein. None of the 3 control groups differed in alpha-lipoprotein cholesterol concentration but in each of the 3 populations the coronary patients tended to have lower alpha values than their controls.

The cholesterol data are compatible with the hypothesis that the 3 populations have different frequency distributions of cholesterol values, the coronary patients in each population tending to be drawn from the upper end of the corresponding population distribution, with no general critical level distinguishing all coronary patients as a total group.

In the past several years coronary patients in the Twin Cities tend to be so frequently on diets or drugs to control cholesterol that it is increasingly difficult to find patients who may properly characterize the natural history of the disease. The patients reported here were free from this complication.

Acknowledgment

We are grateful to Dr. Mario Mattioli in Naples and Drs. Reuben Berman and Ernst Simonson in Minneapolis for their aid in providing patients for study. Dr. Mario Mancini greatly aided the laboratory work in Naples. Cholesterol analyses in Minneapolis were carried out under the supervision of Dr. Joseph T. Anderson and Mrs. Nedra Foster.

Summario in Interlingua

Subjectos mascule de minus que 66 annos de etate qui suffreva inequivocamente de morbo cardiac coronari in le "Citates Gemine" de St. Paul e Minneapolis in Minnesota e in Neapole in Italia esseva comparate con clinicamente normal subjectos mascule de correspondente typos de domicilio, etates, occupationes, e stato socio-economic.

Le patientes in le Citates Gemine (N=numero total =72) non differeva in le relative peso corporee ab le gruppo de controlo (N=338), e le relative peso medie del duo gruppos esseva minus que illos in tanto

le un e le altere del duo gruppos coronari in Neapole como etiam le gruppo de controlo de classe socio-economic superior in Neapole. Le relative peso corporee medie del patientes coronari de classe socio-economic superior in Neapole (N=54) esseva insignificativemente superior a illo del correspondente gruppo de controlo (N=89). Le patientes coronari de classe obrer in Neapole (N=54) tendeva significativemente a portar pesos excessive in comparation con le correspondente gruppo de controlo (N=144).

Le concentration seral de cholesterol total esseva significativemente plus alte in ambe le gruppos in le Citates Gemine que in tanto le un como etiam le altere gruppo de controlo in Neapole, e le patientes coronari in le Citates Gemine differeva in iste respecto con alte grados de signification ab le subjectos de controlo in le Citates Gemine. Sed mesmo le subjectos de controlo in le Citates Gemine habeva plus alte valores que le patientes coronari in Neapole. Finalmente, in ambe le gruppos socio-economic in Neapole, le patientes habeva plus alte nivellos medie de cholesterol que le correspondente subjectos de controlo. In le caso del classe obrer in Neapole, le separation in obreros manual e sedentari revelava nulle differentia in relative peso corporee e nulle in le nivello seral de cholesterol.

Le differentias del nivellos de cholesterol seral esseva causate per le cholesterol in lipoproteina beta. Nulle del 3 gruppos de controlo differeva ab le altere 2 in le concentration del cholesterol de lipoproteina alpha, sed in cata un del 3 populationes le patientes coronari tendeva a exhibir plus basse valores alpha que le correspondente gruppos de controlo.

Le datos relative a cholesterol es compatibile con le hypothese que le 3 populationes ha differente distributiones frequential del valores de cholesterol e que in cata un del populationes le patientes coronari tende a pertiner in le area superior del correspondente distribution de population, sin que un nivello critic existe con validitate general pro le distinction de omne le patientes coronari como gruppo total.

In le curso del passate annos, le patientes coronari in le Citates Gemine tende si frequentemente a viver sub regimes dietari o drogal visante a reducer lor nivellos de cholesterol que il deveni de plus in plus difficile trovar patientes qui characterisa directemente le historia natural del morbo. Le patientes del presente reporto es exempte ab iste complication.

References

1. Barr, D. P., Russ, E. M., and Eder, H. A.: Protein relationships in human plasma. II. In atherosclerosis and related conditions. Am. J. Med. **11**: 480, 1951.
2. Gertler, M. M., Garn, S. M., and Lerman, J.: The interrelationships of serum cholesterol, cholesterol esters and phospholipids in health and in coronary artery disease. Circulation **2**: 205, 1950.
3. Oliver, M. F., and Boyd, G. S.: The plasma lipids in coronary artery disease. Brit, Heart J. **15**: 387, 1953.
4. Nikkilä, E.: Studies on the lipid-protein relationships in normal and pathological sera and the effect of heparin on serum lipoproteins. Scandinav. J. Clin. & Lab. Invest. **5**: Suppl. 8, 1953, 101 pp.
5. Gertler, M. M., White, P. D., and Others: Coronary Heart Disease in Young Adults. Cambridge, Mass., Harvard University Press, 1954, 218 pp.
6. Oliver, M. F., and Boyd, G. S.: Serum lipoprotein patterns in coronary sclerosis and related conditions. Brit. Heart J. **17**: 299, 1955.
7. Biörck, G., Blomquist, G., and Sievers, J.: Cholesterol values in patients with myocardial infarction and in a normal control group. Acta med. scandinav. **150**: 493, 1957.
8. Lawry, E. Y., Mann, G. V., Peterson, A., Wysocki, A. P., O'Connell, R., and Stare, F. J.: Cholesterol and beta lipoproteins in the serum of Americans. Am. J. Med. **22**: 635, 1957.
9. Oliver, M. F.: Coronary disease, hypercholesterolemia and its treatment. Scottish M. J. **3**: 225, 1958.
10. Dodds, C., and Mills, G. L.: Influence of myocardial infarction on plasma lipoprotein concentration. Lancet **1**: 1160, 1959.
11. Technical Group of the Committee on Lipoproteins and Atherosclerosis: Evaluation of serum lipoprotein and cholesterol measurements as predictors of clinical complications of atherosclerosis. Circulation **14**: 691, 1956.
12. Dawber, T. R., Moore, F. E., and Mann, G. V.: Coronary heart disease in the Framingham study. Am. J. Pub. Health **47**: 4, 1957.
13. Doyle, J. T., Heslin, A. S., Hilleboe, H. E., Formel, P. F., and Korns, R. F.: A prospective study of degenerative cardiovascular disease in Albany: Report of three years' experience. Am. J. Pub. Health **47**: 25, 1957.
14. —, de Lalla, L. S., Baker, W. H., Heslin, A. S., and Brown, R. K.: Serum lipoproteins in pre-clinical and in manifest ischemic heart disease. J. Chron. Dis. **6**: 33, 1957.
15. —, Heslin, A. S., Hilleboe, H. E., and Formel, P. F.: Early diagnosis of ischemic heart disease. New England J. Med. **261**: 1096, 1959.
16. Keys, A.: The cholesterol problem. Voeding, Amsterdam **13**: 539, 1952.
17. —: Prediction and possible prevention of coronary disease. Am. J. Pub. Health **43**: 1399, 1953.
18. —: Diet and the epidemiology of coronary heart disease. J.A.M.A. **164**: 1912, 1957.
19. —, Kimura, N., Kusukawa, A., Bronte-Stewart, B., Larsen, N. P., and Keys, M. H.: Lesson

from serum cholesterol studies in Japan, Hawaii and Los Angeles. Ann. Int. Med. **48**: 83, 1958.

22. BRONTE-STEWART, B., KEYS, A., AND BROCK, J. F.: Serum cholesterol, diet and coronary heart disease. Lancet **269**: 1103, 1955.

23. PAGE, I. H., LEWIS, L. A., AND GILBERT, J.: Plasma lipids and proteins and their relationship to coronary disease among Navajo Indians: Circulation **13**: 675, 1956.

24. TOOR, M., KATCHALSKY, A., AGMON, J., AND ALLALOUF, D.: Serum-lipids and atherosclerosis among Yemenite immigrants in Israel. Lancet **1**: 1270, 1957.

25. SCRIMSHAW, N. S., TRULSON, M., TEJADA, C., HEGSTED, D. M., AND STARE, F. J.: Serum lipiprotein and cholesterol concentrations: comparisons of rural Costa Rican, Guatemalan and United States populations. Circulation **15**: 805, 1957.

24. LARSEN, N. P.: Diet and atherosclerosis. Arch. Int. Med. **100**: 436, 1957.

25. PADMAVATI, S., GUPTA, S., AND PANTULU, G. V. A.: Dietary fat, serum cholesterol levels and incidence of atherosclerosis and hypertension in Delhi, India. Am. Heart J. **56**: 112, 1958.

26. BROCK, J. F.: Nutrition and the clinician. Lancet **2**: 923, 1959.

27. SHAPER, A. G., AND JONES, K. W.: Serum-cholesterol, diet and coronary heart disease in Africans and Asians in Uganda. Lancet **2**: 534, 1959.

28. WOLFE, M. S. DE., AND WHYTE, H. M.: Serum cholesterol and lipoproteins in natives of New Guinea and Australians. Australasian Ann. Med. **7**: 47, 1958.

29. ASSOCIATION OF LIFE INSURANCE MEDICAL DIRECTORS AND ACTUARIAL SOCIETY OF AMERICA. Medico-Mortality Investigations. Vol. 1, New York, 1912.

30. ARMSTRONG, D., DUBLIN, L., WHEATLEY, G., AND MARKS, H.: Obesity and its relation to health and disease. J.A.M.A. **147**: 1007, 1951.

31. SOCIETY OF ACTUARIES: Build and blood pressure study. Vol. 1. Chicago, Society Actuaries, 1959, 208 pp.

32. KEYS, A.: Obesity and degenerative heart disease. Am. J. Pub. Health **44**: 864, 1954.

33. —: Obesity and heart disease. J. Chron. Dis. **1**: 456, 1955.

34. —: Weight changes and health of men. *In* Weight Control. Edited by E. S. Eppright, P. Swanson, and C. A. Iverson. Ames, Iowa, Iowa State College Press, 1955, Chap. 8.

35. ANDERSON, J. T., AND KEYS, A.: Cholesterol in serum and lipoprotein factions. Clin. Chem. **2**: 145, 1956.

36. ABELL, L. L., LEVY, B. B., BRODIE, B. B., AND KENDALL, F. E.: A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. J. Biol. Chem. **195**: 357, 1952.

37. RIVIN, A. U., YOSHINO, J., SHICKMAN, M., AND SCHJEIDE, O. A.: Serum cholesterol measurement—hazards in clinical interpretation. J.A.M.A. **166**: 2108, 1958.

38. KEYS, A., ANDERSON, J. T., AND GRANDE, F.: Serum-cholesterol response to dietary fat. Lancet **1**: 787, 1957.

39. —, FIDANZA, F., AND KEYS, M. H.: Further studies on serum cholesterol of clinically healthy men in Italy. Voeding, Amsterdam **16**: 492, 1955.

40. —, KIMURA, N., KUSUKAWA, A., AND YOSHITOMI, M.: Serum cholesterol in Japanese coal miners. Am. J. Clin. Nutrition **5**: 245, 1957.

41. PABRAI, P. R., AND SEHRA, K. B.: Lipoprotein cholesterol in coronary disease and anemia. Current Sc. **27**: 163, 1958.

42. WATKIN, D. M., LAWRY, E. Y., MANN, G. V., AND HALPERIN, M.: A study of serum beta-lipoprotein and total cholesterol variability and its relation to age and serum level in adult human subjects. J. Clin. Invest. **33**: 874, 1954.

43. THOMAS, C. B., AND EISENBERG, F. F.: Observations on the variability of total serum cholesterol in Johns Hopkins medical students. J. Chron. Dis. **6**: 1, 1957.

44. —, AND MURPHY, E. A.: Further studies on cholesterol levels in the Johns Hopkins Medical students: the effect of stress and examinations. J. Chron. Dis. **8**: 661, 1959.

45. HAMMARSTEN, J. F., CATHEY, C. W., REDMOND, R. F., AND WOLF, S.: Serum cholesterol, diet, and stress in patients with coronary artery disease. Abstracted, J. Clin. Invest. **36**: 897, 1957.

46. FRIEDMAN, M., ROSENMAN, R. H., AND CARROLL, V.: Changes in the serum cholesterol and blood clotting time in men subjected to cyclic variation of occupational stress. Circulation **17**: 852, 1958.

47. WESTLAKE, P. T., WILCOX, A. A., HALEY, M. I., AND PETERSON, J. E.: Relationship of mental and emotional stress to serum cholesterol levels. Proc. Soc. Exper. Biol. & Med. **97**: 163, 1958.

48. EPSTEIN, F. H., BOAS, E. P., AND SIMPSON, R.: The epidemiology of atherosclerosis among a random sample of clothing workers of different ethnic origins in New York City. J. Chron. Dis. **5**: 300, 1957.

49. KEYS, A., MICKELSEN, O., MILLER, E. v. O., HAYES, E. R., AND TODD, R. L.: The concentration of cholesterol in blood serum of normal man and its relation to age. J. Clin. Invest. **29**: 1347, 1950.

50. FORSSMAN, O., AND LINDEGARD, B.: The post-coronary patient. J. Psychosomatic Res. **3**: 89, 1958.

51. THOMAS, A. J., COCHRANE, A. L., AND HIGGINS, I. T. T.: The measurement of the prevalence of ischemic heart disease. Lancet 2: 540, 1958.
52. KEYS, A., KARVONEN, M. J., AND FIDANZA, F.: Serum-cholesterol studies in Finland. Lancet 2: 175, 1958.
53. YATER, W. M., TRAUM, A. H., BROWN, W. G., FITZGERALD, R. P., GEISLER, M. A., AND WILSON, B. B.: Coronary artery disease in men 18 to 39 years old. Am. Heart J. 36: 334, 1948 .
54. MASTER, A. M., JAFFE, H. L., AND CHESKY, K.: Relationship of obesity to coronary disease and hypertension. J.A.M.A. 153: 1499, 1953.
55. CHAPMAN, J. M., GOERKE, L. S., DIXON, W, LOVELAND, D. B., AND PHILLIPS, E.: Clinical status of a population group in Los Angeles under observation for two to three years. Am. J. Pub. Health 47: 33, 1957.
56. DRAKE, R. M., BUECHLEY, R. W., BRESLOW, R. W., AND BRESLOW, L.: An epidemiological investigation of coronary heart disease in the California Health Survey population. Am. J. Pub. Health 47: 43, 1957.
57. BUECHLEY, R. W., DRAKE, R. M., AND BRESLOW, L.: Height, weight, and mortality in a population of longshoremen. J. Chron. Dis. 7: 36, 1958.

Immortality

A plant or vegetable consumed to ashes to a contemplative and school-Philosopher seems utterly destroyed, and the form to have taken his leave for ever; but to a sensible Artist the forms are not perished, but withdrawn into their incombustible part, where they lie secure from the action of that devouring element. This is made good by experience, which can from the Ashes of a Plant revive the plant, and from its cinders recall it into its stalk and leaves again. What the Art of man can do in these inferiour pieces, what blasphemy is it to affirm the finger of GOD cannot do in these more perfect and sensible structures. This is that mystical Philosophy, from whence no true Scholar becomes an Atheist, but from the visible effects of nature grows up a real Divine, and beholds not in a dream, as Ezekiel, but in an ocular and visible object, the types of his resurrection.—SIR THOMAS BROWNE. *Religio Medici.* Edited by W. A. Greenhill, M.D. London, Macmillan and Co., Ltd., 1950, p. 76.

Physiologic Studies in Congenital Absence of the Left Main Pulmonary Artery

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CONGENITAL ABSENCE of a main pulmonary artery branch is now a well-recognized clinical entity, more than 60 cases having been reported in the literature. Diagnosis has heretofore been based primarily on radiologic findings[1] in both routine x-rays and angiocardiography. Physiologic studies of pulmonary function, including differential bronchospirometry, however, provide valuable diagnostic information in addition to demonstrating the unusual behavior of a lung possessing normal ventilatory capacity despite grossly abnormal circulation. Few studies of this nature have been published.[2] The present report of 2 such patients with congenital absence of the left pulmonary artery provides new physiologic data in these cases of such extreme imbalance of ventilation and perfusion.

Case Reports

Case 1

G. P., a 27-year-old white man was first seen in 1950 at the age of 22 years for evaluation of hemoptysis and weight loss of 14 pounds. Decreased breath sounds and rales were heard over the left upper lobe, patchy densities in the left lung field were seen radiologically, and a diagnosis of resolving pneumonitis was made. Bronchoscopy showed bronchial inflammation and bronchography was normal.

Since 1950 several episodes of hemoptysis had occurred. Extensive studies had been performed to rule out pulmonary tuberculosis and bronchiectasis. Pulmonary function studies in 1954 are presented in table 1. Maximum breathing capacity and lung volume studies were entirely normal. Exercise studies on a treadmill were also within normal limits, alveolar-arterial oxygen difference being 23 mm. Hg. Bronchospirometry findings (table 2) were grossly abnormal, showing only 7 per cent oxygen uptake on the left side. Carbon dioxide production was 37 per cent of the total on the left, and ventilation was approximately normal for both right and left lungs. During bronchospirometry peripheral arterial blood samples showed 94 per cent oxyhemoglobin saturation when room air was breathed and 74 per cent when the right catheter lumen was occluded for 1 minute. With the left lumen occluded the patient was perfectly comfortable for several minutes. When he breathed pure nitrogen through the right lumen and room air through the left, oxyhemoglobin saturation dropped to 54 per cent in slightly more than 1 minute. During breathing of nitrogen through the left lumen of the catheter, however, the saturation dropped to 87 per cent after 3½ minutes.

On the basis of these findings a diagnosis of absence of the left main pulmonary artery was made, which was confirmed by angiocardiography (fig. 1). On bronchoscopic examination prominent vascular pulsations were noted in the submucosal region on the left, but no definite bleeding point was seen.

Because of repeated severe hemoptyses the left lung was removed in 1957. At operation the degree of bronchial arterial circulation to the left lung was very impressive (fig. 2). These vessels originated from both posterior and anterior aspects of the mediastinum and reached the lung through adhesive bands located at the apex of the left upper lobe, tip of the lingula, and inferior pulmonary ligament. There was no aortic arch on the left side. The pulmonary veins were considered normal.

A radiograph of the resected lung after injection of methylglucamine diatrizoate (Renografin) into the systemic bronchial circulation demonstrated these numerous dilated vessels (fig. 3).

Case 2

J. S., a 28-year-old white man was first seen in 1953 because of unusual fatigue of 8 months' duration and left-sided chest pain, increasing on deep breathing and particularly after hard work.

In 1946 x-rays had shown blunting of the left costophrenic angle and subsequently a left-sided fibrinous pleurisy developed, but no evidence of active tuberculous infection had been found.

Physical examination on admission to the hospital revealed only decreased breath sounds and

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Supported in part by funds made available by the Vermont Heart Association.

Table 1

Pulmonary Function Studies

Case no.	MBC l./min.	TVC % 3 min.	TLC l.	VC l.	FRC l.	ERV l.	RV l.	Mixing index	Resting O_2 Sat. %	Exercise O_2 Sat. %	Alveolar-arterial O_2 Diff. mm. Hg	Exercie D_{CO} ml./min./mm. Hg
1.	141	—	5.2	4.2	1.8	0.85	0.96	1.2	94	91	23	—
2.	122	100	6.1	4.4	2.7	1.08	1.64	1.0	96	96	6	24

MBC, maximum breathing capacity; TVC, timed vital capacity; TLC, total lung capacity; VC, vital capacity; FRC, functional residual capacity; ERV, Expiratory reserve volume; RV, residual volume, D_{co}, diffusing capacity of carbon monoxide.

Table 2

Bronchospirometric Studies

Case no.	Ventilation, % total R	Ventilation, % total L	O_2 uptake, % total R	O_2 uptake, % total L	CO_2 prod., % total R	CO_2 prod., % total L	Vital cap. % total R	Vital cap. % total L	Art. Sat., % N_2 to left lung	Art. Sat., % N_2 to right lung	Minim. calc., bronchial flow ml./min.	CO uptake, ml./min. R	CO uptake, ml./min. L
1.	48	52	93	7	63	37	65	35	87	54	1838	—	—
2.	65	35	95	5	74	26	71	29	95	80 (30 sec.)	1810	.94	.43

increased tactile fremitus in the left mid-lung field posteriorly. Pulmonary function studies revealed maximum breathing capacity, timed vital capacity, and lung volume determinations to be normal (table 1). Exercise tolerance test on a treadmill was normal. Alveolar-arterial difference was only 6 mm. Hg. Bronchospirometry (table 2) demonstrated that 35 per cent of the total ventilation was being accomplished on the left side. On the left oxygen consumption was 5 per cent of the total, carbon dioxide production was 26 per cent, and 29 per cent of the total vital capacity was produced on this side. Arterial oxyhemoglobin saturation was 96 per cent, both at rest and on exercise. While breathing pure nitrogen on the left side for 5 minutes the patient maintained oxyhemoglobin saturation at 95 per cent. When the nitrogen was introduced on the right side, however, saturation fell to 80 per cent after only 30 seconds.

Bronchography showed crowding of the bronchial subdivisions of the left lung and markedly hyperemic bronchial mucosa. Diagnosis of absence of the left main pulmonary artery branch was made and was confirmed by angiocardiography (fig. 4).

Bronchospirometry in 1958 again showed 35 per cent of total ventilation, 5 per cent of oxygen uptake, and 26 per cent of carbon dioxide production being performed on the left side. Differential diffusing capacity for carbon monoxide was tested and 30 per cent uptake of carbon monoxide by the left lung was demonstrated. Diffusing capacity during exercise at a steady state was normal, 24 ml. per minute per mm. Hg.[3]

Discussion

Congenital absence of a main branch of a pulmonary artery without associated intracardiac defects has been reported less than 20 times, the majority of cases having involvement of the right pulmonary artery. Aortic anomalies are very frequently associated with the absence of the pulmonary artery. An attractive recent embryologic explanation for the combination of anomalies is that of Anderson et al.,[4] who suggested that proximal interruption of the pulmonary arch with persistence of a primitive pulmonary artery per se accounts for the final picture. This theory is consistent with, and readily explains all the variations of absent pulmonary artery that have been seen.

Diagnosis in the past has usually rested on a combination of radiographic and clinical findings, angiocardiography providing definite confirmation in several instances prior to thoracotomy.[1, 5–7] Surprisingly enough, pulmonary function studies, and in particular bronchospirometric investigation, have very seldom been utilized to their full extent. These procedures are not only valuable diagnostically, but provide important physiologic data regarding ventilation and accessory perfusion of the lung deprived of its normal circulation

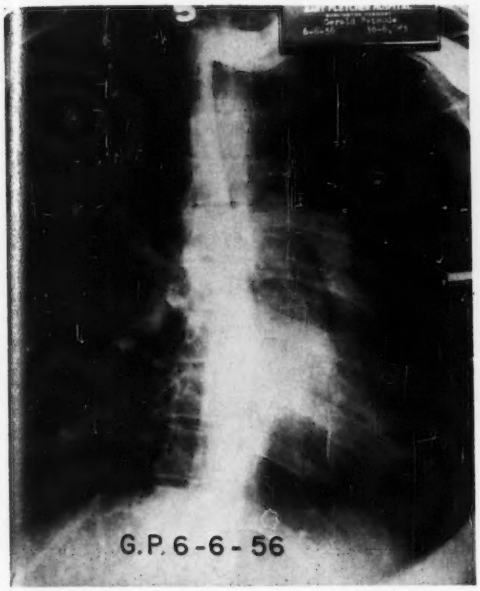

Figure 1

Venous angiocardiogram in case 1. Filling of right pulmonary artery is seen with absence of filling on the left.

As has been previously demonstrated the ventilation of a lung without a pulmonary artery may be considerable and even normal. This is true in the present 2 cases, in which the affected lungs accounted for 52 and 35 per cent, respectively, of the total ventilation.

To our knowledge studies of carbon dioxide production in such lungs have not been previously reported. In the present examinations this information was obtained by collecting expired air from each lumen of the Carlen's bronchospirometric catheter and analyzing it in the Scholander microgas apparatus. The results, showing carbon dioxide productions by the affected lungs of 37 and 26 per cent, suggest a considerable degree of collateral circulation to these ventilated lungs. The presence of such a circulation has been discussed by others[4, 6, 8] and is convincingly demonstrated in figures 2 and 3. That such large amounts of carbon dioxide are capable of being excreted from an arterial circulation is easily explained by the shape of the carbon dioxide dissociation curve.

Figure 2

Extensive systemic arterial circulation on lung surface at time of pneumonectomy in case 1.

Further evidence for a richly developed accessory circulation to these lungs is presented by the differential bronchospirometric oxygen uptake studies. Although it has generally been reported[2, 5, 9] or assumed that little or no oxygen uptake occurs, in our cases the values were unequivocally significant even during the breathing of room air and with normal arterial oxyhemoglobin saturation. Some earlier studies in this regard[2, 10] are qualified by the use of anesthesia and the presence of hypoventilation and arterial desaturation. Arterial blood normally but not 100 per cent saturated, will obviously absorb additional oxygen when perfused through an adequately ventilated lung with a higher alveolar oxygen tension.

The observation of a drop in oxyhemoglobin saturation from normal to 87 per cent in one of our patients during the breathing of pure nitrogen on the affected side (table 2) is in effect an expression of oxygen excretion and once again shows that oxygen exchange occurs in this lung. We are unable to explain the absence of desaturation in the second patient under similar circumstances; we suspect that his effective bronchial blood flow is not so large as the first patient's. This appears rea-

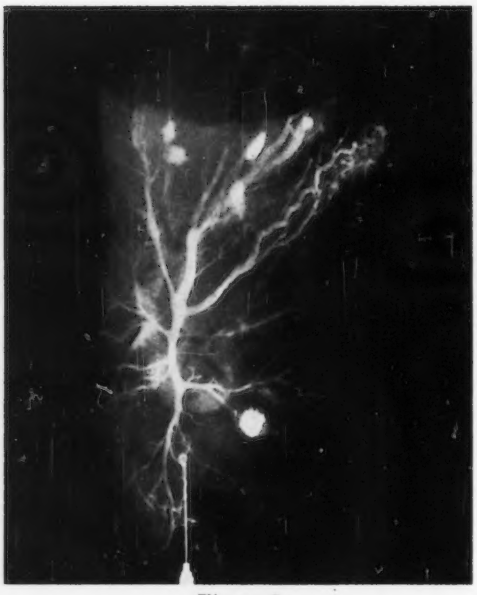

Figure 3

X-ray of resected lung in case 1 after injection of radiopaque dye into arteries of systemic circulation.

sonable in view of the absence of hemoptysis.

As reasoned by Bloomer,[10] the Fick principle may be utilized for calculation of bronchial blood flow. By use of the absolute uptake of oxygen by the affected lung, the simultaneously determined arterial oxyhemoglobin content and capacities, and on the assumption that the bronchial blood reaching the lung has the same saturation as brachial artery blood, *minimal* bronchial blood flow may be calculated. These minimal flows in our patients were calculated as 1,838 and 1,810 ml. Were blood leaving the affected lung less than 100 per cent saturated, as is probably the case, the calculated flow would be significantly higher. Despite such an increased left ventricular work load, our patients exhibited neither radiologic or electrocardiographic evidence of left ventricular hypertrophy nor clinical signs of cardiac decompensation.

With normal or nearly normal ventilatory dynamics in the absence of alveolar-capillary membrane block, diffusing capacity for carbon

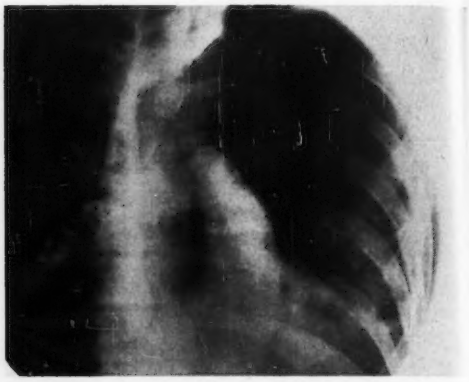

Figure 4

Venous angiocardiogram in case 2. Absence of filling of left pulmonary artery is noted.

monoxide would be expected to be normal. This was indeed the case in our one patient so tested who showed a steady state D_{co} of 24 ml. per minute per mm. Hg, which is within normal limits for his age.[3] Although it is not feasible to determine the diffusing capacity of each lung separately, carbon monoxide uptake on each side (table 2) is in good agreement with the values of differential ventilation. This lends further credence to recently published work[11] that diffusing capacity is closely related to ventilation.

Summary

Physiologic studies in 2 cases of congenital absence of the left pulmonary artery are presented. The significance of carbon dioxide production and oxygen uptake in the affected lung and their relationship to ventilation and perfusion are discussed. All functional and anatomic evidence points to a highly significant bronchial artery circulation substituting in part for the absent pulmonary artery.

Summario in Interlingua

Studios physiologic in 2 casos de absentia congenit del arteria sinistro-pulmonar es presentate. Es discutite le signification del production de bioxydo d carbon e del captation de oxygeno in le afficite pul mon e le relation de illos al functionamento del ven tilation e del perfusion. Omne le disponibile dato functional e anatomic suggere le existentia de u significativissime circulation de arteria bronchial qu age in vicariato partial del absente arteria pulmonar

References

1. WYMAN, S. M.: Congenital absence of a pulmonary artery: its demonstration by roentgenography. Radiology **62**: 321, 1954.
2. MADOFF, I. M., GAENSLER, E. A., AND STRIEDER, J. W.: Congenital absence of the right pulmonary artery. New England J. Med. **247**: 149, 1952.
3. HANSON, J. S., AND TABAKIN, B. S.: Carbon monoxide diffusing capacity in normal male subjects age 20-60 during exercise. J. Appl. Physiol. **15**: 402, 1960.
4. ANDERSON, R. C., CHAR, F., AND ADAMS, P.: Proximal interruption of a pulmonary arch (absence of one pulmonary artery): case report and a new embryologic interpretation. Dis. Chest **34**: 73, 1958.
5. STEINBERG, I., DOTTER, C. T., AND LUKAS, D. S.: Congenital absence of a main branch of the pulmonary artery. J.A.M.A. **152**: 1216, 1953.
6. HERZENBERG, H., RUDHE, U., AND IVEMARK, B. I.: Congenital hypoplasia of the right pulmonary artery associated with myomatosis of the lung, Acta chirurg. Scandinav. **Suppl. 245**: 323, 1959.
7. STEINBERG, I.: Congenital absence of a main branch of the pulmonary artery. Am. J. Med. **24**: 559, 1958.
8. ELDER, J. C., BROFMAN, B. L., KOHN, P. M., AND CHARMS, B. L.: Unilateral pulmonary artery absence or hypoplasia. Circulation **17**: 557, 1958.
9. SMART, J., AND PATTINSON, J. N.: Congenital absence of left pulmonary artery. Brit. M. J. **1**: 491, 1956.
10. BLOOMER, W. E., HARRISON, W., LINDSKOG, G. E., AND LIEBOW, A. A.: Respiratory function and blood flow in bronchial artery after ligation of pulmonary artery. Am. J. Physiol. **157**: 317, 1949.
11. LEWIS, B. M., LIN, T-H., NOE, F. E., AND KOMISARUK, R.: The measurement of pulmonary capillary blood volume and pulmonary membrane diffusing capacity in normal subjects; the effects of exercise and position. J. Clin. Invest. **37**: 1061, 1958.

William Beaumont recognized, grasped, and improved the opportunity which fell in his path, with a zeal and an unselfishness not excelled in the annals of medical science. . . . His work remains a model of patient, persevering investigation, experiment, and research, and the highest praise we can give him is to say that he lived up to and fulfilled the ideals with which he set out and which he expressed when he said: "Truth, like beauty, when unadorned, is adorned the most, and, in prosecuting these experiments and inquiries, I believe I have been guided by its light."—SIR WILLIAM OSLER. *Aphorisms from His Bedside Teachings and Writing.* Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 110.

Common Circulatory Measurements in Smokers and Nonsmokers

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CURIOSITY about the effects of tobacco smoking on the circulation has been renewed since the appearance of data showing higher cardiovascular mortality rates in smokers than in nonsmokers.[1, 2] As yet, no convincing theoretical or experimental basis has been established for this difference. The acute effects of smoking on the circulation are, of course, well known, being reflected in increased pulse rate and arterial blood pressure, and reduced peripheral blood flow. They have long been thought to be partly mediated through nicotine as stimulus for nervous release of epinephrine and pituitary "vasopressin," and there is recent supportive evidence for this belief in the demonstration of increased epinephrine excretion during smoking.[3] Tobacco smoking influences coronary circulation, myocardial metabolism, over-all metabolic activity, and oxygen-carrying capacity of the blood.[4-6] It is conceivable that the pressor and other acute effects of smoking might aggravate or rarely precipitate manifest heart disease, but consideration of these effects does not provide a reasonable basis for conjecture about the role of smoking in the underlying pathogenesis of coronary or other heart disease. For example, there is no evidence for a direct influence of smoking on atherogenesis or thrombogenesis.

The chronic "effects" of smoking are particularly difficult to study experimentally, but comparison of physiologic characteristics in long-term habitual smokers and nonsmokers is one available approach. We have studied associations of a number of cardiovascular, respiratory, and metabolic items with smoking habit.[7-10] Admittedly, this approach may disguise interesting and significant individual responses, and such investigations reveal associations but do not establish cause and effect. The present paper is concerned with resting pulse rate and blood pressure and circulatory reactions to several pressor stimuli in male smokers and nonsmokers. Acute effects of smoking have been largely excluded. Related variables of age, relative body weight, and basal oxygen consumption are considered.

Data are presented for 4 groups, a total of 1,093 men, ages 17 to 67 years: study A, a group of 286 middle-aged business and professional men, ages 45 to 55; study B, 159 male university students, ages 17 to 25; study C, 414 railroad employees, ages 25 to 67; study D, 234 Minneapolis firemen, ages 25 to 63.

Smoking Classification

Standardized questionnaires regarding smoking were administered by the Laboratory staff. Data were grouped for analysis, under the following categories of *cigarette* smoking:

1. Never smoked cigarettes
2. Occasionally—not daily
3. Light—under 10 cigarettes per day
4. Moderate—11 to 20 cigarettes per day
5. Heavy—21 or over cigarettes per day
6. Stopped—stopped *all* smoking for at least 1 year

The over-all intensity category of cigarette smoking was assigned largely on the basis of the prior 5- to 10-year period, the level of smoking during the immediately preceding year serving as principal reference point.

If cigar, or pipe, or both, were the only type of smoking and were light or remote (1 cigar or less a day or 5 pipes or less per day

From the Laboratory of Physiological Hygiene, University of Minnesota, and the Medical Department, Mutual Service Insurance Companies, St. Paul, Minn.

Supported in part by grants from the National Heart Institute, National Institutes of Health, (grant H 10 (C 12)), U. S. Public Health Service, and the Tobacco Industry Research Committee, New York, N. Y.

the subject was considered for our purposes in the "never smoked" category. Consideration of multiple smoking habits in these groups failed to modify importantly the distribution of categories of smoking intensity, nor were the mean values in combined smoking categories substantially different from those obtained for cigarette categories alone. Results in all groups will thus be given only in terms of intensity of cigarette smoking. Individuals who successfully stopped *all* forms of smoking one or more years prior to the year of these measurements are considered under the "stopped" category.

Study A

In study A a cross-sectional analysis of circulatory and related items was made according to smoking category in a group of 286 business and professional men, ages 45 to 55 at the outset (mean age 49.5), who have served as subjects in a longitudinal cardiovascular study, now in its thirteenth year. The original sample of 300 men was selected as previously described.[9] Data are reported for the 233 subjects remaining after clinical screening (for heart disease, abnormal electrocardiograms, and arterial blood pressure of 160 systolic, 95 diastolic, or both) and for the entire group of 286 men for whom all data were available.

Acute effects of smoking were well controlled in study A, with both a written and telephonic request not to smoke on the morning when the subjects, highly motivated and cooperative, were to report to the laboratory. Smoking was prohibited during the morning procedures concerned with cardiovascular measurements.

Basal pulse rate, basal oxygen consumption, resting blood pressure, and pulse and blood pressure responses to the cold pressor test, carbon dioxide inhalation, and physical work were determined.

Basal heart rate and oxygen consumption were measured in the early morning after 20 to 30 minutes rest in a darkened air-conditioned room. The relative body weight was calculated from standard Medico-Actuarial tables for subjects measured in light trunks and without shoes. Resting blood pressures were taken in the supine position 3 times during the course of physical examination, and are reported as an average.

To perform the cold pressor test, carbon dioxide inhalation, and work tests, the subjects walked from the basal metabolism room to a nearby air-conditioned room. They observed tests being carried out on their predecessors, then relaxed 5 minutes in bed while procedures were further explained. An electrocardiogram was recorded and pulse and blood pressures taken "until stable." The right hand was immersed to the wrist for 1 minute in a wide-mouth Thermos bucket of ice water. Pulse and blood pressure were taken at 15 to 30 seconds and 45 to 60 seconds. Greatest pulse and systolic and diastolic blood pressure increments during the immersion period were used in the analysis. The 5-minute recovery pulse rate and blood pressure measurements were used as baseline values for the subsequent test, in which 6 per cent carbon dioxide in air was inhaled for 5 minutes. The greatest pulse, and systolic and diastolic blood pressure increments during this period were used for the analysis. After recovery from the carbon dioxide test the subject walked to another air-conditioned room and watched his predecessor performing the work test. Pulse and blood pressure readings were then made after standing for 1 minute. The treadmill, moving at 3.5 mph, 5° grade, was boarded for a 15-minute walk. A mean of 3 pulse and blood pressure recordings between 10 and 15 minutes of the walk were employed for statistical analysis, as well as the 1- and 3-minute recovery values for the pulse rate. Recovery blood pressures were not analyzed because of inaccuracies we have found in the auscultatory measurement of blood pressure during recovery from work.[11]

Study B

A similar analysis was made in a group of 159 healthy male university students ages 17 to 25 (mean 20.6 years) for the same cardiovascular items. The technical procedures

were the same as those followed in the older group, as was the exclusion of acute effects of smoking.

Study C

Resting pulse, work pulse taken from 9 to 10 minutes during a 10-minute treadmill walk at 3.5 mph, 5 per cent grade, and resting blood pressure were measured in a sample of 414 railroad switchmen, clerks, and dispatchers, ages 25 to 67, mean age 46.8 years. The switchmen were self-selected volunteers, the clerks a randomly chosen sample from the general offices of 3 railroad companies, and the dispatchers represent approximately 85 per cent of all railway dispatchers in a 6-state area. Smoking was not rigorously controlled, but the program of activities was such that an x-ray, physical examination, and 10-minute rest immediately preceded the cardiovascular determinations, during which time smoking was proscribed. Age trends were analyzed for pulse and blood pressure and slopes were compared between categories of "never" and "heavy" cigarette smokers.

Study D

Resting pulse and blood pressure were recorded in 234 firemen, the *total* manpower of randomly selected Minneapolis firestations. The subjects' ages were 25 to 63, with a mean age of 37.2 years. This was a field study, and smoking was not controlled prior to the first contact. Pulse and blood pressure were measured following a ballistocardiogram or electrocardiogram, however, during which the subjects had rested supine without smoking for at least 30 minutes. Pulse and blood pressure were measured in the right arm, in the seated position. Analysis of age trends was made for pulse and blood pressure in "never" and "heavy" cigarette smoking categories.

Results

Study A

The age range of this group is limited to 1 decade. Table 1 shows means for all items according to intensity of smoking habit. Mean age and relative body weight are similar in the 5 smoking categories. Rarely are there consistent trends in this data from "never" up to "heavy" smoking categories, but this may be partly due to the small and heterogeneous group of "occasional" and "light" smokers.

Small trends are apparent with increasing smoking intensity in the cold pressor pulse increment (upward), cold pressor diastolic blood pressure increment (downward), the pulse and systolic blood pressure increments during carbon dioxide inhalation (upward), and in the actual exercise pulse rate (upward). In general, the mean differences are small.

The extremes of smoking habit are compared in table 2, "never" versus "heavy" smokers, with statistical tests of the differences in means. There is a higher basal oxygen consumption in heavy smokers, and the difference approaches statistical significance. Basal pulse rate is higher in the heavy smokers but not significantly so. The diastolic blood pressure increment on the cold pressor test is not so great in the smokers, and the difference almost reaches the 5 per cent level of statistical significance. The only item of clearly significant difference is the greater systolic blood pressure rise (4.7 mm. Hg) in smokers during carbon dioxide inhalation.

It was of interest to enlarge the group numbers by combining *all* smokers, and this is done in table 3 for the circulatory items in which differences between "never-heavy" groups either approached statistical significance (table 2) or manifested progressive trends according to intensity category of smoking (table 1). The result is a difference between "never" and all smokers in basal oxygen consumption and cold pressor response, and elimination of significance for difference in the systolic blood pressure change during carbon dioxide inhalation.

In table 4 the entire group of 286 men, "normal" and "abnormal," is considered. Mean values and the significance of mean differences are shown only for those items that showed significant differences, or nearly so, between "never" and "heavy" smoking categories. The higher pulse rate in smokers as well as differences in cold pressor response,

Table 1

Mean Values and Standard Deviations of Several Cardiovascular Items in the "Normal" Sample of 233 Middle-Aged Men, Smokers and Non-smokers

Smoking category	Never (N = 67)		Occasional and light (N = 28)		Moderate (N = 52)		Heavy (N = 36)		Stopped (N = 50)	
	M	SD	M	SD	M	SD	M	SD	M	SD
Age (years)	49.2	3.1	48.6	2.7	49.3	3.2	48.4	2.9	49.6	3.6
Relative body weight (per cent)	100.3	14.8	101.1	14.7	98.2	13.0	98.9	14.7	99.6	13.3
Basal oxygen consumption (cc. O_2/min./M.^{2})	113.3	11.6	112.8	9.8	120.3	12.9	117.9	11.4	113.1	10.1
Basal pulse (beats 1 min.)	64.7	8.5	63.7	10.3	65.3	7.9	67.2	7.6	65.0	9.1
Mean resting blood pressure										
Systolic (mm. Hg)	123.0	11.3	122.4	10.9	122.7	4.2	124.0	12.0	124.2	16.9
Diastolic	81.1	6.3	82.5	6.1	81.2	7.7	83.1	7.5	83.5	8.8
Cold pressor response increments										
Pulse (beats/min.)	5.2	4.1	5.2	3.7	5.5	5.1	6.9	7.0	5.8	4.8
Systolic BP (mm. Hg)	19.8	11.9	18.4	11.9	18.8	11.0	19.7	10.2	18.3	10.8
Diastolic BP (mm. Hg)	15.1	8.3	13.8	7.6	12.5	7.3	12.0	6.6	15.2	9.7
CO_2 inhalation response increments										
Pulse (beats/min.)	7.8	7.7	8.4	6.0	9.4	5.4	9.3	6.8	8.4	7.4
Systolic BP (mm. Hg)	15.3	9.6	16.1	8.0	17.8	10.6	20.0	13.4	18.8	14.1
Diastolic BP (mm. Hg)	9.7	6.5	7.6	4.9	9.6	7.0	11.5	7.0	10.7	6.8
Actual exercise pulse (beats/min.)	114.8	13.7	114.9	12.8	118.7	14.6	120.5	15.1	118.1	16.5
Exercise response increments										
Pulse (beats/min.)	53.2	11.3	55.0	11.7	57.0	12.5	56.4	10.3	55.7	12.3
Systolic BP (mm. Hg)	5.4	12.5	4.2	8.9	5.2	7.7	5.3	7.9	6.9	9.0
Diastolic BP (mm. Hg)	−1.3	6.0	−0.7	5.9	−2.0	7.3	0.3	3.9	0.6	5.5
Recovery as increments over pre-exercise level										
Pulse after 30 sec. (beats/min.)	27.9	11.2	30.4	10.2	31.5	11.6	30.5	9.8	29.7	10.9
Pulse after 3 min. (beats/min.)	13.6	7.8	10.3	5.3	12.6	8.3	12.8	6.1	12.2	8.3

Table 2

Mean Values and F Tests of Significance of Mean Differences ($\overline{\Delta}$) between "Never" and "Heavy" Smokers for Cardiovascular Items in "Normal" Sample of 233 Middle-Aged Men

Item	Smoking category	No.	M	SD	$\overline{\Delta}$	F
Age (years)	Never	67	49.2	3.1	−0.8	1.6
	Heavy	36	48.4	2.8		
Relative body weight (per cent)	Never	67	100.3	14.8	−1.4	<1.0
	Heavy	36	98.9	14.6		
Basal oxygen consumption (cc. O_2/min./M.^{2})	Never	67	113.3	11.6	+4.6	3.7*
	Heavy	36	117.9	11.4		
Basal pulse (beats/min.)	Never	67	64.7	8.5	+2.5	2.1
	Heavy	35	67.2	7.6		
Mean resting blood pressure (mm. Hg)						
Systolic	Never	60	123.0	11.3	+1.0	<1.0
	Heavy	33	124.0	12.0		
Diastolic	Never	60	81.1	6.3	+2.0	1.8
	Heavy	33	83.1	7.5		
Cold pressor responses, as increments						
Pulse (beats/min.)	Never	67	5.2	4.1	+1.7	2.3
	Heavy	35	6.9	7.0		
Systolic BP (mm. Hg)	Never	67	19.8	11.9	−0.1	<1.0
	Heavy	35	19.7	10.2		
Diastolic BP (mm. Hg)	Never	67	15.1	8.3	−3.1	3.6*
	Heavy	35	12.0	6.6		
CO_2 inhalation responses, as increments						
Pulse (beats/min.)	Never	67	7.4	7.7	+1.9	1.6
	Heavy	36	9.3	6.8		
Systolic BP (mm. Hg)	Never	67	15.3	9.6	+4.7	4.3†
	Heavy	36	20.0	13.4		
Diastolic BP (mm. Hg)	Never	67	9.7	6.6	+1.8	1.6
	Heavy	36	11.5	7.0		
Actual exercise pulse (beats/min.)	Never	52	114.8	13.6	+5.4	2.6
	Heavy	28	120.2	15.1		
Exercise responses, as increments						
Pulse (beats/min.)	Never	50	53.2	11.3	+3.2	1.5
	Heavy	28	56.4	10.2		
Systolic BP (mm. Hg)	Never	49	5.4	12.5	−0.1	<1.0
	Heavy	26	5.3	7.9		
Diastolic BP (mm. Hg)	Never	49	−1.3	6.0	+1.6	1.4
	Heavy	26	+0.3	3.8		
Recovery after exercise, as increments over pre-exercise level						
Pulse after 30 sec. (beats/min.)	Never	50	27.9	11.2	+2.6	1.0
	Heavy	28	30.5	9.8		
Pulse after 3 min. (beats/min.)	Never	50	13.6	7.8	−0.8	<1.0
	Heavy	28	12.8	6.1		

*Approaches 5 per cent level of significance.

†Reaches or exceeds 5 per cent level of significance.

Table 3

Mean Values and F Tests of Significance of Mean Differences ($\overline{\Delta}$) between "Never" and "All Smokers" Combined for Selected Cardiovascular Measurements in 233 Middle-Aged Men

Item	Smoking category	No. of men	M	SD	$\overline{\Delta}$	F
Basal oxygen consumption (cc. O_2/min./M.^{2})	Never	67	113.3	11.6	+4.4	5.9*
	All smokers	114	117.7	12.0		
Basal pulse (beats/min.)	Never	67	64.7	8.5	+0.8	0.4
	All smokers	110	65.5	8.5		
Cold pressor response, as increment						
Diastolic BP (mm. Hg)	Never	67	15.1	8.3	−2.4	4.3*
	All smokers	115	12.7	7.1		
Co_2 inhalation response, as increment						
Pulse (beats/min.)	Never	67	7.4	7.7	+1.7	2.8
	All smokers	112	9.1	6.0		
Systolic BP (mm. Hg)	Never	67	15.3	9.6	+2.8	3.0
	All smokers	112	18.1	11.0		
Actual exercise pulse (beats/min.)	Never	52	114.8	13.7	+3.5	2.0
	All smokers	94	118.3	14.3		
Exercise pulse increment (beats/min.)	Never	50	53.2	11.3	+3.1	2.4
	All smokers	94	56.3	11.6		

*Reaches or exceeds 5 per cent level of significance.

carbon dioxide test, and work pulse rates, are in the same direction and usually exaggerated by addition of the subjects with cardiovascular abnormalities.

Study B

Table 5 presents mean values and standard deviations for the same series of circulatory measurements according to smoking habit in the group of 159 young, healthy male university students. Smoking habit was obviously of much shorter duration in this group, and there are some differences in age and relative body weight between smoking categories, the smokers being less "overweight." The faster basal pulse rate in smokers is again found, but in table 6 it is apparent that there are no statistically significant differences in the circulatory items between "never" smokers and "all smokers" combined.

It is of interest to compare the mean values of tables 1 and 5 between younger and older men (study A and B) for the same measurements, without regard to smoking habit. Basal oxygen consumption is considerably higher in all the young men, resting systolic blood pressure only slightly lower, and the diastolic blood pressure much lower than in the middle-aged men. The young men showed far less rise in heart rate on exercise, and much greater change in pulse pressure than the middle-aged men, and the pulse recovery after exercise was much faster. The systolic pressure response to the cold pressor test is clearly greater in middle-age. These age differences in rest and in circulatory response to work and cold are well known.

Throughout the analyses for study A and study B, the Behrens-Fisher test[12] was applied when the variance of values for groups compared for smoking habit was not homogeneous. The significance of the differences previously indicated by the F tests is not altered.

Study C

Table 7 presents the mean values for resting and work pulse, and blood pressures for the nonsmokers and heavy smokers of the railroad sample. No statistical comparison of these means is given at this point, because of the different mean age in smoking groups and the wide spread in age. It appears, however, that relative body weight and resting

Table 4

Mean Values for Those Circulatory Items in Which Differences between "Never" and "Heavy" Smokers Reach or Approach Statistical Significance, among the Total Sample of 286 Middle-Aged Men, "Normal" and "Abnormal"

Item	Smoking category	No. of men	M	SD	$\overline{\Delta}$	F
Basal oxygen consumption (cc. O_2/min./M.^{2})	Never	82	114.7	13.1	+4.5	3.7*
	Heavy	49	119.2	12.6		
Basal pulse (beats/min.)	Never	82	64.5	8.4	+4.5	7.6†
	Heavy	48	69.0	9.9		
Cold pressor response, as increment Diastolic BP (mm. Hg)	Never	82	15.8	8.8	−4.1	7.9†
	Heavy	47	11.7	6.5		
Co_2 inhalation response, as increment Systolic BP (mm. Hg)	Never	82	16.1	10.0	+5.0	5.7‡
	Heavy	47	21.1	13.4		
Actual exercise pulse (beats/min.)	Never	61	114.8	13.0	+6.9	5.2‡
	Heavy	35	121.7	16.2		

*Approaches 5 per cent level of significance.

†Reaches or exceeds 1 per cent level of significance.

‡Reaches or exceeds 5 per cent level of significance.

Table 5

Mean Values and Standard Deviations of Several Cardiovascular Items in 159 Male University Students, Smokers and Nonsmokers

Smoking category	Never (N = 83)		Light (N = 23)		Moderate + heavy (N = 53)	
	M	SD	M	SD	M	SD
Age (years)	20.1	1.9	20.6	1.9	20.8	1.8
Relative body weight (%)	108.5	14.8	102.3	12.0	104.9	15.3
Basal oxygen consumption (cc. O_2/min./M.^{2})	128.4	10.2	133.5	25.3	125.8	10.5
Basal pulse (beats/min.)	62.7	8.8	63.6	6.8	65.7	7.1
Mean resting BP (mm. Hg)						
Systolic	121.3	9.4	118.9	8.7	120.3	8.3
Diastolic	68.1	9.2	67.8	9.1	69.4	9.5
Cold pressor increments						
Pulse (beats/min.)	5.3	5.6	5.7	4.9	6.2	8.6
Systolic BP (mm. Hg)	14.6	7.8	14.1	6.8	13.2	8.9
Diastolic BP (mm. Hg)	13.4	8.0	14.9	9.6	14.1	7.2
CO_2 inhalation increments						
Pulse (beats/min.)	10.2	7.2	11.5	8.3	9.4	8.0
Systolic BP (mm. Hg)	11.4	6.7	14.0	6.6	12.1	7.3
Diastolic BP (mm. Hg)	12.0	7.5	12.8	6.4	9.7	6.0
Actual exercise pulse (beats/min.)	118.6	14.3	119.5	14.8	115.7	9.0
Exercise response increments						
Pulse (beats/min.)	39.4	10.1	42.2	13.7	40.0	8.4
Systolic BP (mm. Hg)	16.3	10.6	13.5	8.5	17.6	9.6
Diastolic BP (mm. Hg)	−18.8	4.4	−18.0	13.8	−17.0	14.2
Recovery as increments over pre-exercise level						
Pulse after 30 secs. (beats/min.)	6.2	10.5	11.0	13.4	6.6	7.3
Pulse after 3 min. (beats/min.)	3.9	9.9	6.8	11.1	4.4	8.4

Table 6

Comparison of Several Cardiovascular Items in Student Men Smokers and Nonsmokers. Differences of Means ($\overline{\Delta}$) and F Tests of Significance in "Never" versus "All Smokers." ($n_1 + n_2 - 2 = 57$)

	$\overline{\Delta}$	F
Age (years)	+0.6	4.2*
Relative body weight (%)	—4.4	3.7†
Basal oxygen consumption (cc. O_2/min./M.^{2})	−0.2	<1.0
Basal pulse (beats/min.)	+2.3	2.4
Mean resting blood pressure (mm. Hg)		
Systolic	−1.4	1.0
Diastolic	+0.9	<1.0
Cold pressor increments		
Pulse (beats/min.)	+0.7	<1.0
Systolic BP (mm. Hg)	−1.2	<1.0
Diastolic BP (mm. Hg)	+1.0	<1.0
CO_2 inhalation increments		
Pulse (beats/min.)	−0.1	<1.0
Systolic BP (mm. Hg)	+1.5	<1.0
Diastolic BP (mm. Hg)	−1.0	<1.0
Actual exercise pulse (beats/min.)	−1.8	<1.0
Exercise response increments		
Pulse (beats/min.)	+0.6	<1.0
Systolic BP (mm. Hg)	+0.1	<1.0
Diastolic BP (mm. Hg)	−1.5	<1.0
Recovery as increments over pre-exercise level		
Pulse after 30 secs. (beats/min.)	+1.7	1.0
Pulse after 3 min. (beats/min.)	+1.2	<1.0

*Reaches or exceeds 5 per cent level of significance.
†Approaches 5 per cent level of significance.

blood pressures are distinctly lower in the heavy smokers. Mean values for these circulatory items were grouped by age decades and tests of significance of the slopes, or age trends, are given in table 8. The regression equations are not given in order to reduce the number of tables; however, significant age trends for blood pressure are found, and are positive, as expected, and an age trend for the resting pulse, also positive, is apparent in the heavy smokers. No significant age trend in exercise pulse rate is found.

Comparison between smokers and nonsmokers is made in table 9 by analysis of the differences in the age trend slopes and their intercepts. The greater rise in the resting pulse rate with age among heavy smokers is the only statistically significant difference.

Table 7

Mean Values and Standard Deviations for Age, Relative Body Weight, Resting and Exercise Pulse, and Blood Pressure in Railroad Workers, "Never" and "Heavy" smokers

Smoking category	Never (N = 73)		Heavy (N = 138)	
	M	SD	M	SD
Age (years)	46.8	12.1	43.4	10.3
Relative body weight (%)	105.9	11.5	103.1	12.5
Resting pulse rate (beats/min.)	68.1	11.9	69.3	12.3
Actual exercise pulse rate (beats/min.)	115.7	12.7	116.6	13.9
Resting blood pressure (mm. Hg)				
Systolic	133.8	18.4	129.3	17.8
Diastolic	80.6	9.8	77.5	12.3

Study D

Table 10 shows mean values for resting pulse and blood pressure in the firemen. The mean age is similar in smoking categories for this sample. Again, no statistical comparison of means is made, but the same tendency prevails between smokers and nonsmokers as in the other groups studied. The nonsmokers have somewhat greater relative body weight, while heavy smokers have higher resting heart rates and lower blood pressures. In table 11, significant age trends in blood pressure are also apparent in this sample, and are positive, and comparison of the slopes in smokers and nonsmokers is made in table 12. Again, the higher resting pulse in smokers is the only statistically significant difference (significant difference in intercepts, table 12).

Discussion

Resting pulse rate is higher in smokers of most groups studied, and the cause is not apparent. The significant positive age trend in pulse rate among heavy smokers exists only in the mixed railroad worker population. There is evidence from other sources that the intensity of smoking decreases with age after a peak between ages 25 and 34,[13] so that an increase in amount of smoking with age is not likely a factor in the pulse-age trend. The acute cardio-accelerator effects of smoking were largely eliminated in the perform-

Table 8

Cardiovascular Characteristics in Railroad Employees, "Never" and "Heavy" Smokers. F Tests of Significance of Age Trends (Slopes). ($n_1 + n_2 - 2 = 209$)

Smoking category	Never F	Heavy F
Resting pulse rate	<1	9.9*
Actual exercise pulse rate	<1	<1
Systolic blood pressure	18.0†	15.9†
Diastolic blood pressure	7.9*	25.3†

*Reaches or exceeds 1 per cent level of significance.
†Reaches or exceeds 0.1 per cent level of significance.

Table 9

Cardiovascular Characteristics in Railroad Employees, "Never" versus "Heavy" Smokers. F Tests of the Differences in Age Trends Studied Cross-Sectionally

Age trend characteristic	Slope F	Intercept F	Over-all difference F
Resting pulse rate	4.1*	1.0	2.5
Systolic blood pressure	<1	1.1	<1
Diastolic blood pressure	2.5	1.5	2.0
Actual exercise pulse rate	1.7	<1	1.0

*Reaches or exceeds 5 per cent level of significance.

ance of these studies, and such effects rarely last over 30 minutes after cigarette smoking.[14, 15] Unmodified nicotine is no longer present in the body a few hours after experimental administration.[16] There is also evidence that habitual smokers have no greater over-all epinephrine excretion than nonsmokers so that other factors than smoking must be more important in total epinephrine secretion.[3] If the faster heart rate is due to smoking, the cause must lie in the increased metabolic activity, for which there is some evidence here, or in the repetitive or chronic effects of nicotine on autonomic regulation, or respiratory function. It may be roughly estimated, with several assumptions, that the difference in metabolic rate found in study A (table 4) might account for half of the pulse rate difference.

The heart rate during work and the time of its recovery on stopping work are important measures of the functional integrity, "fitness," of the circulation. There is a tendency for smokers in the middle-aged group of study A to have a faster work pulse, greater pulse increment during work, and slower pulse recovery. This cannot here be related to relative obesity. The difference in work pulse becomes statistically significant when those subjects with cardiovascular disease are included (table 4). The safe, trite, but unsatisfactory conclusion of many investigators concerned with smoking and health is that, "people with heart disease should not smoke, or at least should cut down." No difference in work heart rates is found between smokers and nonsmokers of the young student group, study B, or the railroad workers, study C. The data herein provide no convincing evidence for deterioration of cardiovascular "fitness" in smokers. They are consistent with the reports on acute effects of smoking on work performance and "fitness."[17]

Differences are found in resting blood pressure in study C and D (lower systolic and diastolic blood pressure in smokers) and are statistically significant ($p = < 0.05$) when the groups are combined and rendered homogeneous with regard to age. There is no such tendency in study A and B, groups highly selected at the outset with respect to elimination of subjects with hypertension. The manner of selection of the study group is apparently a factor in these differences, as relative hypotension in smokers has

Table 10

Mean Values and Standard Deviations for Age, Relative Body Weight, Pulse Rate, and Blood Pressure in Minneapolis Firemen, "Never" and "Heavy" Smokers

Smoking category	Never (N = 56) M	Never (N = 56) SD	Heavy (N = 60) M	Heavy (N = 60) SD
Age (years)	39.8	9.5	39.9	6.4
Relative body weight (per cent)	112.0	10.8	108.6	10.4
Resting pulse rate (beats/min.)	72.3	8.3	79.8	12.0
Resting blood pressure (mm. Hg)				
Systolic	135.1	20.6	132.4	14.8
Diastolic	80.2	12.5	76.5	10.0

Table 11

Cardiovascular Characteristics in Firemen, "Never" and "Heavy" Smokers. F Tests of Significance of Age Trends (Slopes). ($n_1 + n_2 - 2 = 114$)

Smoking category	Never F	Heavy F
Resting pulse rate	1.6	<1
Systolic blood pressure	8.3*	7.0*
Diastolic blood pressure	<1	8.4*

*Reaches or exceeds 1 per cent level of significance.

Table 12

Cardiovascular Characteristics in Firemen, "Never" versus "Heavy" Smokers. F Tests of the Differences in Age Trends Studied Cross-Sectionally. ($n_1 + n_2 - 2 = 114$)

Age trend characteristic	Slope F	Intercept F	Over-all difference F
Resting pulse rate	<1	15.2*	—
Systolic blood pressure	<1	<1	<1
Diastolic blood pressure	3.5	<1	1.8

*Reaches or exceeds 0.1 per cent level of significance.

been found in other, broader population studies.[8, 18]

Other differences in composition of the groups may play a role in the apparent blood pressure differences between smokers and nonsmokers. In the combined groups C and D there is a highly significant difference in relative body weight according to smoking habit ($p = < 0.001$). "Never" smokers are relatively more obese (mean relative body weight = 108.5 per cent, n = 129) than "heavy" smokers (mean relative body weight = 104.7 per cent, n = 198). It is quite possible that this is a partial explanation for the blood pressure differences. If the data for study C and D are combined and standardized for relative body weight, the mean differences in blood pressure between heavy smokers and nonsmokers are no longer significant ($p = > 0.10$).

If there were a different prevalence of hypertension among smokers and nonsmokers, or different smoking habits among hypertensive and normotensive subjects, selection bias might well explain the mean blood pressure differences. Brown, McKeown, and Whitfield found "hypertension" (over 200 mm. Hg systolic or 100 mm. Hg diastolic) in 18.2 per cent of "never" smokers and 13.8 per cent of "current" smokers in a large sample of men in the seventh decade. Chi-square testing of their data, however, revealed that these differences might be due to chance (P chi square = 0.11). In our combined samples A, C, and D, we find "hypertension" (defined differently, as 140 mm. Hg systolic or 90 mm. Hg diastolic, or over) in 30.5 per cent of "never" smokers and 26.3 per cent of "current" smokers. However, this difference, in the same direction, is statistically nonsignificant (P chi square = 0.43). Thus, there is a tendency toward more "hypertensive" subjects among nonsmokers, and more nonsmokers among groups with hypertension, but the differences are not statistically significant.

If smoking is a causative factor in heart disease, it does not appear to operate through a relationship to high blood pressure or obesity, both of which have been found clearly associated with excess mortality rate for heart disease. It is difficult to conceive that the small mean differences in blood pressure, or relative body weight, in the direction toward lower values in smokers, relate to the epidemiologic fact of higher cardiovascular mortality rates in smokers.

In direct comparisons of blood pressure responses to pressor stimuli (study A) the diminished diastolic pressure rise on cold exposure in smokers is the only consistently significant difference (tables 2 and 4). The absolute diastolic blood pressure during the cold stimulus is also lower in smokers. We are unaware of experimental evidence that change in small vessel reactivity develops upon chronic administration of nicotine. However, the lower diastolic pressure and diminished response to cold among smokers suggest the possibility of chronic sympathetic blockade or depletion of vascular norepinephrine by nicotine.

The decline in diastolic cold pressor response with age found by Hines[19] is not seen in over-all comparison of the young and middle-aged men of study A and B. As in our

student group, Thomas found no significant difference in cold pressor response of young student smokers and abstainers.[20] It should be borne in mind that students have a short average duration of smoking habit and may not be ideal candidates for cross-sectional comparisons of certain functions with "chronic effects" of smoking as the point of interest.

Basal oxygen consumption is greater in smokers of study A. This has been previously observed[21] and may conceivably relate to the lower relative obesity in smokers that is found consistently throughout the groups studied. Earlier conjecture concerning weight differences in smokers and nonsmokers has invoked psychophysiologic theories of appetite suppression or of oral gratification.

Thus, statistically significant differences between groups of habitual smokers and nonsmokers are found for certain common circulatory measurements. Consistent tendencies for some of the items appear in different populations examined at different times. However, there are inconsistencies in regard to the "effect" of the *amount* of smoking, and sources of bias from selection are apparent that render dubious the etiologic role of smoking in the observed differences. For these reasons, plus the over-all small magnitude of the differences found, we are unable to give serious consideration to these circulatory phenomena as significant underlying causes of increased cardiovascular mortality rate among smokers. This investigative approach does not elucidate the role of individual response characteristics to tobacco smoking. Whether a part of the excess mortality rate in smokers is related to acute pressor and other effects of smoking that might aggravate a latent disease process or precipitate manifest illness or death, is not known.

Summary

Pulse rates and blood pressure, and circulatory responses to pressor stimuli were compared in habitual smokers and nonsmokers in an attempt to ascertain possible "chronic effects" of tobacco smoking on the circulation.

Several common cardiovascular measurements were made in 4 groups, a total of 1,093 men, ages 17 to 67, and comparisons made with reference to the cigarette smoking habit. Acute effects of smoking were eliminated and, when possible, effects of age and weight were eliminated statistically.

Relative body weight is consistently lower in the "heavy" cigarette smokers compared to those who "never" smoked.

Basal oxygen consumption is slightly higher in smokers than in nonsmokers. Pulse rate during work and recovery is significantly higher in one group of middle-aged men if pathologic cases in the group are considered.

In "normal" populations, somewhat preselected for absence of hypertension, no differences in resting blood pressures are found between smokers and nonsmokers. In the broader studies, involving samples of the working population, smoking is associated with lower systolic and diastolic pressures.

Circulatory responses to stimuli of the cold pressor test and carbon dioxide inhalation reveal a small but significant diminished diastolic pressure response to cold and possibly a greater systolic response to carbon dioxide in smokers.

Young student groups, with short duration of smoking habit, show no significant differences between smokers and nonsmokers for these circulatory parameters.

The associations found do not provide evidence for large or important differences in circulatory reactivity between groups of habitual smokers and nonsmokers. There is little evidence for deterioration of cardiovascular "fitness" in smokers performing work tests.

The small magnitude of the differences found in circulatory measurements, plus certain sources of bias which are discussed, preclude serious consideration at present of these factors as underlying causes of the increased mortality rate among smokers. Other questions unanswered concern the importance of individual circulatory responses, individual hypersensitivity to smoking, and the significance of acute pressor and other effects of

smoking on persons with cardiovascular disease, latent or manifest.

Acknowledgment

The technical procedures involved in this study were supervised by Walter Carlson, B.S., and Mrs. Nedra Foster, Administrative Assistant, and the statistical analyses were performed by Mr. Norris Schulz.

Summario in Interlingua

Pro determinar le possibile "effectos chronic" de fumar tabaco super le circulation, fumatores habitual e non-fumatores esseva comparate con respecto al frequentia del pulso, al tension del sanguine, e al responsas circulatori a stimulos pressori.

Plure commun mesurationes cardiovascular esseva effectuate in 4 gruppos con un total de 1.093 subjectos mascule de etates de inter 17 e 67 annos, e comparationes esseva facite con referentia al habitude de fumar cigarrettas. Acute effectos del fumar esseva eliminate. In tanto que possibile, medios statistic esseva usate pro eliminar le effectos de etate e peso.

Le relative peso corporee es uniformemente plus basse in le "forte" fumator de cigarrettas in comparation con le subjectos que fuma "nunquam."

Le consumption basal de oxygeno es levemente plus alte in fumatores que in non-fumatores. Le frequentia del pulso durante le labor e le restablimento es significativemente plus alte in un gruppo de homines de etate medie quando le casos pathologic in le gruppo remane incluse.

In populationes "normal"—pre-seligite in un certe mesura pro absentia de hypertension—nulle differentia esseva notate inter fumatores e non-fumatores con respecto a lor tensiones de sanguine. In plus large studios—con specimens del population travaliante—le fumar es associate con plus basse valores pro le tension systolic e etiam diastolic.

Le responsas circulatori al stimulos del test de frigor pressori e al inhalation de bioxydo de carbon revela un micre sed significative reduction in le responsa del tension diastolic a frigor in le caso del fumatores e possibilemente etiam un plus forte responsa systolic a bioxydo de carbon.

Juvene gruppos de studentes, con curte duration del habitude del fumar, revela nulle significative differentias inter fumatores e non-fumatores con respecto al mentionate parametros circulatori.

Le associationes trovate non provide provas de importante differentias del reactivitate circulatori inter gruppos de fumatores habitual e gruppos de non-fumatores. Il existe pauc evidentia pro le deterioration del "validessa" de fumatores in le execution de tests de labor.

Le micre magnitude del differentias trovate in le mesurationes circulatori—insimul con certe fontes de error (que es discutite)—exclude, a iste tempore, ab omne serie consideration le suggestion que le mentionate factores es le subjacente causas del augmentate mortalitate inter fumatores. Altere questiones que remane sin responsa concerne le importantia del reactiones circulatori individual, le hypersensibilitate individual al fumo, e le signification de acute effectos pressori e altere del fumar in personas con morbo cardiovascular, tanto latente como etiam manifeste.

References

1. Doll, R., and Hill, A. B.: Lung cancer and other causes of death in relation to smoking. Second report on mortality of British doctors. Brit. M. J. 2: 1071, 1956.
2. Hammond, E. C., and Horn, D.: Smoking and death rates—Report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. J.A.M.A. 166: 1294, 1958.
3. Watts, D. J., and Bragg, A. D.: Effect of smoking on the urinary output of epinephrine and norepinephrine in man. J. Appl. Physiol. 9: 275, 1956.
4. Wynder, E. L., Editor: The Biological Effects of Tobacco. Boston, Little, Brown & Co., 1955, p. 63.
5. Bargeron, L. M., Jr., Ehmke, D., Gonlubol, F., Castellanos, A., Sigel, A., and Bing, R. J.: Effect of cigarette smoking on coronary blood flow and myocardial metabolism. Circulation 15: 251, 1957.
6. Roth, G. M.: Tobacco and the Cardiovascular System. Springfield, Ill. Charles C Thomas, Publisher, 1951, 66 pp.
7. Brozek, J., and Keys, A.: Changes of body weight in normal men who stop smoking cigarettes. Science 125: 1203, 1957.
8. Karvonen, M., Keys, A., Orma, E., Fidanza, F., and Brozek, J.: Cigarette smoking, serum cholesterol, blood pressure, and body fatness. Observations in Finland. Lancet 1: 492, 1959.
9. Blackburn, H., Brozek, J., and Taylor, H. L.: Lung volume in smokers and non-smokers. Ann. Int. Med. 51: 68, 1959.
10. —, Orma, E., Härtel, G., and Punsar, S.: Tobacco smoking and blood coagulation: Acute effect on plasma Stypven time. Am. J. M. Sc. 238: 448, 1959.
11. Henschel, A., de la Vega, F., and Taylor, H. L.: Simultaneous direct and indirect blood pressure measurement in man at rest and work. J. Appl. Physiol. 6: 506, 1954.
12. Johnson, P. O.: Statistical Methods in Research. New York, Prentice-Hall, 1949, 377 pp.
13. Haenszel, W., Shimkin, M. B., and Miller, H. P.: Tobacco smoking patterns in the United States. Public Health Monograph No. 45. U. S. Department of Health, Education, and Welfare, U. S. Government Printing Office, Washington, D. C., 1956.

14. HIESTUND, W. A., RAMSEY, H. J., AND HALE, D. M.: The effect of cigarette smoking on metabolic rate, heart rate, oxygen pulse and breathing rate. J. Lab. & Clin. Med. **25**: 1013, 1940.

15. GODDARD, V. R., AND VOSS, J. G.: The immediate effect of cigarette smoking upon basal metabolic rates of university men and women. J. Lab. & Clin. Med. **27**: 787, 1941.

16. GOODMAN, L. S., AND GILMAN, A.: The Pharmacological Basis of Therapeutics (second edition), New York, The MacMillan Company, 1955, p. 622.

17. KARPOVICH, P. V.: Physiology of Muscular Activity. Philadelphia, W. B. Saunders Company, 1953, p. 304.

18. BROWN, R. G., MCKEOWN, T., AND WHITFIELD, A. G. W.: A note on the association between smoking and disease in men in the seventh decade. Brit. J. Prev. Soc. Med. **11**: 162, 1957.

19. HINES, E. A., JR.: The significance of vascular hyperreaction as measured by the cold pressor test. Am. Heart J. **19**: 408, 1940.

20. THOMAS, C. B., AND MURPHY, E. A.: Observations on some possible precursors of essential hypertension and coronary artery disease. VI. Comparison of the circulatory reactivity to the cold pressor test and to the smoking test. Ann. Int. Med. **50**: 970, 1959.

21. SCHLUMM, F.: Nikotinabusus und Grundumsatz. Verhandl. d. deutsch. Gesellsch. Kong. f. inn. Med. **42**: 151, 1930.

To one that hath committed Murther, if the Judge should only ordain a Fine, it were a madness to call this a punishment, and to repine at the sentence, rather than admire the clemency of the Judge. Thus, our offences being mortal, and deserving not only Death, but Damnation, if the goodness of God be content to traverse and pass them over with a loss, misfortune, or disease, what frensie were it to term this a punishment, rather than as extremity of mercy, and to groan under the rod of His Judgments, rather than admire the Scepter of His Mercies! Therefore to adore, honour, and admire Him, is a debt of gratitude due from the obligation of our nature, states, and conditions; and with these thoughts, He that knows them best, will not deny that I adore Him.—SIR THOMAS BROWNE. *Religio Medici.* Edited by W. A. Greenhill, M.D. London, Macmillan and Co., Ltd., 1950, p. 83.

The Direct Effects of Norepinephrine, Epinephrine, and Methoxamine on Myocardial Contractile Force in Man

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ALTHOUGH the direct effects of sympathomimetic amines on myocardial contractile force have been well documented in the experimental animal,[1-7] such data have not previously been obtained in man. The effects of these agents on the cardiac output and arterial pressure of man have frequently been measured.[8-14] However, these two functions may be profoundly modified by numerous other hemodynamic and reflex influences. Accordingly, any conclusions concerning their direct effect on myocardial contractility, based on such measurements alone, must be viewed with caution. Indirect measurements in man have led to diverse and conflicting concepts of the myocardial actions of sympathomimetic amines[8, 10, 15] and to speculations that these agents, particularly norepinephrine, may have different cardiac effects in man and in experimental animals.[16, 17] Aviado[18] and Selzer and Rytand,[19] in recent comprehensive reviews of the cardiovascular effects and therapeutic indications of sympathomimetic amines, concluded that more definitive studies of these agents in man were needed in order to permit their rational clinical use.

In the present study, the direct effects of norepinephrine, epinephrine, and methoxamine on human myocardial contractile force were studied by means of the Walton-Brodie strain-gage arch[20] in patients undergoing thoracotomy. This instrument has been extensively utilized in the study of the effects of drugs on the heart in the dog,[5, 7] and has been found useful in monitoring myocardial contractility during cardiac operations in man.[21, 22]

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Methods

Sympathomimetic amines were administered during operation to 16 patients. They ranged in age from 4 to 40 years, and the average age was 25 years. Eleven of these patients had atrial septal defects, 3 had ventricular septal defects, and 2 had pulmonic stenosis. None had a history of heart failure or severely diminished cardiac reserve. Preanesthetic medications included meperidine (25 to 75 mg.), scopolamine (0.1 to 0.4 mg.) and promethazine (15 to 50 mg.). After intravenous thiopental induction, all patients were maintained under light general anesthesia with nitrous oxide, oxygen, and a muscle relaxant, either succinylcholine or d-tubocurarine. Thiopental and meperidine were administered in small doses to all patients for maintenance of anesthesia. Atropine was given intravenously in doses of 0.2 to 0.4 mg. to 3 patients prior to thoracotomy.

After a median sternotomy had been performed and the pericardium opened, the strain-gage arch was sutured to a convenient area on the right ventricle and the segment of myocardium between the 2 feet of the arch was stretched to about 50 per cent of its diastolic length. Arterial blood pressure was measured through a polyethylene catheter in the left radial artery by means of a Statham pressure transducer. Continuous recordings of blood pressure and myocardial contractile force were made simultaneously with a multichannel oscillograph.

l-Norepinephrine bitartrate (Levophed, Winthrop), *l*-epinephrine bitartrate (Suprarenin, Winthrop), and methoxamine hydrochloride (Vasoxyl, Burroughs-Wellcome) were administered intravenously either by rapid injection or by infusion. Norepinephrine was administered at least once to all 16 patients. In 5 patients methoxamine was administered in a dose sufficient to approximate the diastolic pressure increment produced by norepinephrine. In 6 patients norepinephrine and epinephrine were injected in succession in equal doses. Metaraminol bitartrate (Aramine, Merck, Sharp and Dohme) and mephentermine sulfate (Wyamine, Wyeth) were also used in several patients. All amines, unless stated otherwise, were injected before institution of cardiopulmonary bypass or cannulation of the venae cavae, generally

at a time when the femoral artery was being prepared for cannulation and the heart was not being manipulated. Contractile force and arterial pressure were recorded during a control period before each administration of an amine. The doses of the amines were calculated as the base except for methoxamine, which was calculated as the hydrochloride salt.

Results

The effects of norepinephrine, epinephrine, and methoxamine on right ventricular contractile force (CF), arterial pressure (BP), and heart rate (HR) are shown in table 1. The amplitudes of the contractile force recordings, which are directly proportional to the force applied by the myocardium to the strain-gage arch, were measured in millimeters. Since the height of the contractile force recording depends upon such variables as the direction of placement of the strain-gage arch, the depth of the sutures and the degree of initial tension placed on it,[23] no attempt was made to convert the deflections into grams of force. The amplitude of the oscillographic deflection during the control period was adjusted arbitrarily in each patient and these control values are not, therefore, comparable in the different patients. The percentage change, however, from the control value following the injection of a drug into an individual patient permits meaningful comparisons.

Norepinephrine

The intravenous administration of norepinephrine increased ventricular contractile force in all 15 patients in whom valid measurements were made (figs. 1 and 2). The response was always transient, lasting about 5 minutes. In 1 additional patient (M.T.), no increase in contractile force was observed, but she developed atrial fibrillation during the norepinephrine injection, and the irregularity of the ventricular contractions made accurate measurements of contractile force impossible. This patient continued to have transient episodes of this arrhythmia during the operation, so that its development may not have been related to administration of the amine. As may be noted in table 1, there was considerable variation in the contractile force, arterial pressure, and heart rate responses in the different patients. Similar variability of response to norepinephrine and other amines has been noted in anesthetized animals[5] and probably depends upon such factors as the different responses of patients to the same dose per kilogram of body weight, variations in the depth of anesthesia, the level of circulating catecholamines, the amount of blood loss, and the activity of the sympathetic nervous system. Although there was some correlation between the contractile force and pressure increments produced by norepinephrine, this relationship also varied among patients (fig. 3).

It is interesting that the 3 youngest patients, aged 4 to 8 years, had relatively small increases in contractile force per unit increase in arterial pressure, suggesting that in children the arteriolar bed is relatively more sensitive to sympathomimetic amines than the myocardium. The patient (A.C.) in whom the contractile force rose only 5 per cent in response to norepinephrine, apparently had an elevated contractile force level at the time it was administered, since the contractile force gradually decreased by 40 per cent during the subsequent period of observation. It is possible that this weak response to norepinephrine was related to a high endogenous level of circulating catecholamines, since a typical response to epinephrine was obtained at a later time when the initial contractile force value was lower. The changes in heart rate in the 14 patients with sinus rhythm ranged from an increase of 18 beats per minute to a decrease of 18 beats per minute. These changes in rate were undoubtedly influenced by the variable state of vagal block that resulted from the pre-anesthetic and anesthetic medications, because norepinephrine is known almost always to result in bradycardia in unanesthetized subjects.

Epinephrine

Epinephrine was administered in the same dose as norepinephrine in 6 patients. In 4 instances, myocardial contractile force increased to approximately the same extent as with the norepinephrine injections (figs. 1 and 2). Systolic pressure also increased in

Table 1

Cardiovascular Effects of Norepinephrine, Epinephrine, and Methoxamine

Patient	Diagnosis	Weight (Kg.)	Drug	Dose μg./Kg.	Control CF mm.	Control BP mm. Hg	Control HR beats/min.	Peak Effect CF mm.	Peak Effect BP mm. Hg	Peak Effect HR beats/min.	Change CF %	Change BP mm. Hg	Change HR beats/min.
L. H., 39F	PS	59.1	Norepi.	0.25	13	100/65	96	19	140/90	114	46	40/25	18
			Epi	0.25	12	115/75	90	18	150/95	114	50	35/20	24
			Methox.	34.00	8	120/80	84	9	170/105	96	13	50/25	12
K. B., 31F	VSD	53.8	Norepi.	0.25	9	115/75	72	12	150/100	60	33	35/25	−12
			Epi.	0.25	8	140/80	84	11	160/75	84	38	20/−5	0
			Methox.	55.00	11	110/80	96	10	140/110	90	−9	30/30	− 6
D. A., 29F	PS	41.8	Norepi.	0.25	9	85/56	72	13	135/90	72	44	50/34	0
			Epi.	0.25	9	74/56	78	12	96/67	90	33	22/11	12
			Methox.	50.00	10	64/50	78	10	96/72	78	0	32/22	0
S. C., 30F	ASD	58.5	Norepi.	0.14	19	112/68	96	22	144/94	108	16	32/26	12
			Methox.	34.00	19	120/72	96	19	136/96	96	0	16/24	0
			Norepi.	0.20	18	128/80	96	24	172/112	102	33	44/32	6
			Methox.	68.00	17	112/72	96	20	168/120	92	18	56/48	− 4
R. T., 24M	ASD	65.0	Norepi.	Inf.*	8	64/36	102	15	168/120	72	88	104/84	−30
H. L., 27F	ASD	43.1	Norepi.	Inf.	17	108/80	102	21	170/136	120	24	62/56	18
			Norepi.	Inf.	17	112/76	100	21	170/144	116	24	58/68	16
S. G., 4F	ASD	12.7	Norepi.	0.38	14	95/70	108	17	130/85	96	21	35/15	−12
S. S., 25F	VSD	42.2	Norepi.	0.25	25	100/63	72	34	113/75	66	36	13/12	− 6
C. T., 8F	ASD	22.8	Norepi.	Inf.	16	120/70	126	19	180/110	126	19	60/40	0
			Methox.	90.00	16	118/80	132	16	130/110	114	0	12/30	−18
			Methox.	120.00	16	118/80	126	15	160/115	108	−6	42/35	−18
J. B., 28M	ASD	57.6	Norepi.	0.14	21	95/60	60	26	120/80	48	24	25/20	−12
A. S., 31M	ASD	68.9	Norepi.	0.23	8	100/64	80	13	148/88	70	63	48/22	−10
C. R., 8F	ASD	22.2	Norepi.	Inf.	17	135/88	126	19	165/104	108	12	30/16	−18
			Methox.	90.0	14	115/80	120	14	180/105	126	0	65/25	6
E. S., 40F	ASD	56.9	Norepi.	0.14	35	100/70	64	42	112/80	60	20	12/10	− 4
A. C., 30F	ASD	41.7	Norepi.	0.25	41	85/50	68	43	105/60	56	5	20/10	−12
			Methox.	48.00	30	80/48	76	28	100/60	64	−7	20/12	−12
			Epi.	0.25	25	90/55	76	34	115/60	76	36	25/5	0
W. P., 15M	VSD	66.4	Norepi.	0.12	35	122/65	75	42	138/78	60	20	16/13	−15
			Epi.	0.12	32	120/62	60	40	105/55	80	25	−20/−7	20
M. T., 28F	ASD	62.5	Norepi.	0.13	Arrhythmia								
			Epi.	0.13	9	65/30	78	12	85/35	78	33	20/5	0

P.S., pulmonary stenosis; VSD, ventricular septal defect; ASD, atrial septal defect, CF, cardiac force; BP, blood pressure; HR, heart rate.

*Infusion of solution containing 4 mg. of norepinephrine/500 ml.

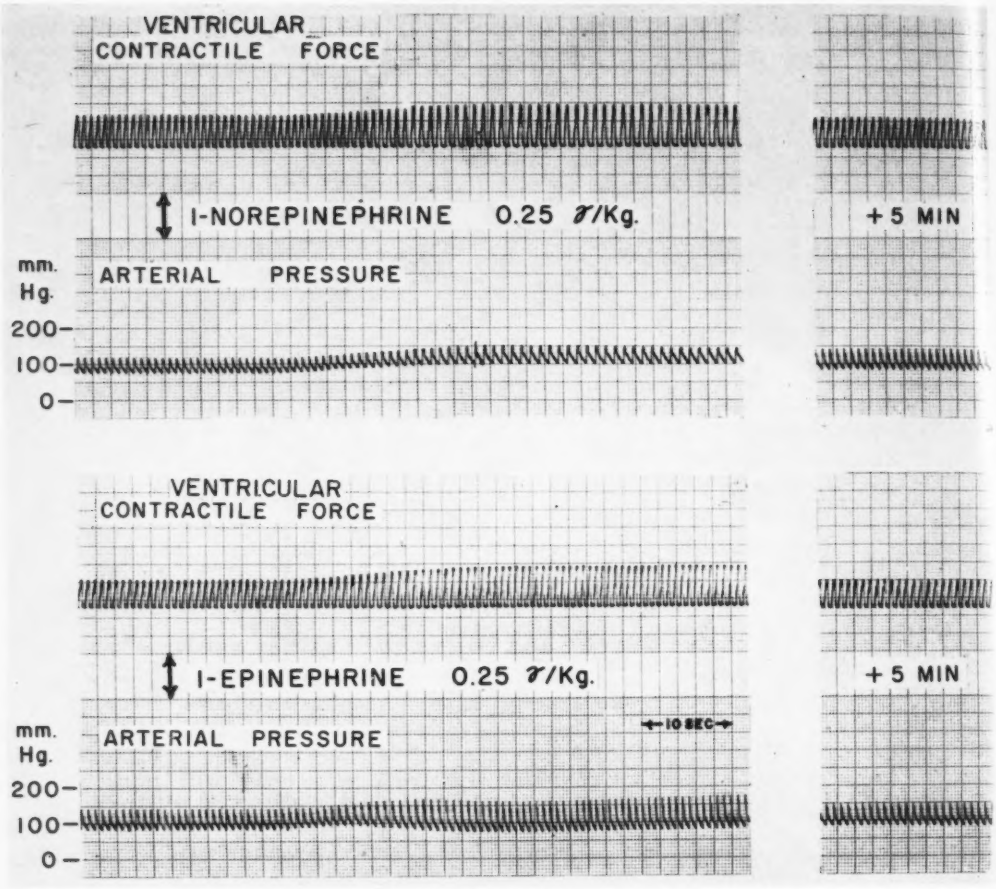

Figure 1

The effects of 0.25 μg./Kg. norepinephrine and epinephrine on right ventricular contractile force and arterial pressure in a 31-year-old patient with ventricular septal defect.

5 of the patients, but the change in diastolic pressure was variable, ranging from a decline of 7 mm. Hg to an increase of 20 mm. Hg. This difference is apparent in figures 1 and 2; in one instance, the diastolic pressure fell approximately 5 mm. Hg in the presence of a contractile force increment of 38 per cent; in the other patient (fig. 2), however, after an unstable initial period the diastolic pressure rose 20 mm. Hg and the contractile force increased 50 per cent. The heart rate either increased up to 24 beats per minute or remained unchanged after epinephrine administration. The duration of the effects of this amine was similar to those produced by norepinephrine.

Methoxamine

This drug was administered to 7 patients (figs. 2 and 3). In 5 of these, contractile force either did not change significantly or decreased slightly (–6 to –9 per cent); in the remaining 2 patients, there were slight increases in contractile force (13 and 18 per cent). The heart rate fell by 4 to 18 beats per minute in 4 of the patients and the rate did not change or increased slightly (6 and 12 beats per minute) in the others. The duration of the pressor effect following a single injec-

tion of methoxamine was usually between 10 and 15 minutes. The pronounced differences between the effects of methoxamine and norepinephrine on contractile force are shown in figure 3. As shown in figure 2, 0.25μg. per Kg. of norepinephrine increased myocardial contractile force 46 per cent and the arterial pressure rose by 40/25 mm. Hg. Methoxamine in a dose of 2 mg.) in this same patient produced an identical increment in diastolic arterial pressure but contractile force increased only 13 per cent.

Mephentermine and Metaraminol

Mephentermine (5 mg.) was administered intravenously to patient L.H. and contractile force increased 71 per cent; the arterial blood pressure increased from 100/70 to 125/80 mm. Hg. This amine was also given in a dose of 15 mg. to an additional patient who had profound hypotension (65/25 mm. Hg) and who is not included in table 1. The blood pressure rose to 110/85 and contractile force increased 30 per cent. The duration of these effects of mephentermine exceeded 15 minutes in each patient.

Metaraminol was administered to 2 patients prior to cardiopulmonary bypass. In patient D.A. a dose of 1 mg. increased contractile force by 75 per cent while the arterial pressure rose from 90/60 to 160/95 mm. Hg. In a second patient, not included in the table, the administration of 1 mg. of metaraminol resulted in a contractile force increment of 43 per cent with an increase in arterial pressure from 80/50 to 125/75 mm. Hg. This drug (0.5 mg.) was also administered to patient S.G. following the repair of an atrial septal defect when hypotension (50/30 mm. Hg) suddenly developed. Contractile force increased 90 per cent and the arterial pressure rose to 108/76 mm. Hg. The duration of the effects of this amine also exceeded 15 minutes.

Discussion

The results of the clinical studies described above demonstrate that epinephrine, norepinephrine, mephentermine, and metaraminol substantially increase myocardial contractile force in man. Injections of norepinephrine and of epinephrine, in the same patients and in equal doses, resulted in almost identical increments in myocardial contractile force. Methoxamine, on the other hand, had virtually no effect on myocardial contractile force in doses that produced pronounced increases in arterial pressure. These results are similar to those previously reported in anesthetized [5, 7] and unanesthetized dogs[6] and demonstrate that there are no qualitative differences in the effects of these amines on contractile force in man and the dog.

Previous studies in man have consistently demonstrated that epinephrine augments cardiac output[8-10] and that norepinephrine either does not change or diminishes this function.[8, 10, 11, 13, 14] These results have led to the erroneous conclusion that norepinephrine is an amine with a purely pressor action and with no effect on myocardial contractility,

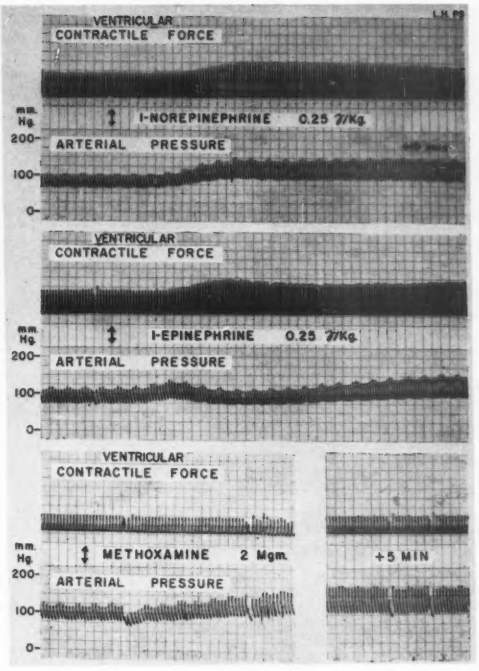

Figure 2

The effects of 0.25 μg./Kg. of norepinephrine and epinephrine and of 2 mg. (34 μg./Kg.) of methoxamine on right ventricular contractile force and arterial pressure in a 39-year-old patient with pulmonary stenosis.

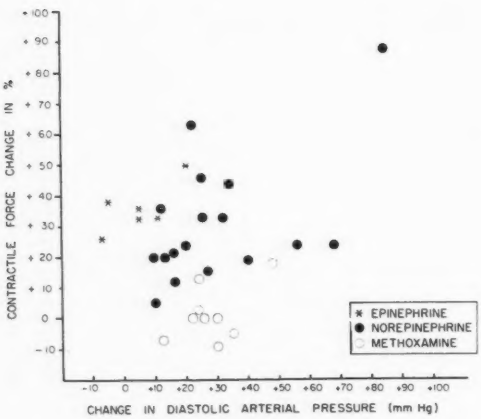

Figure 3

Relationships between the changes in diastolic arterial blood pressure and myocardial contractile force that occurred after each administration of sympathomimetic amines in 16 patients.

but that epinephrine is a stimulant of myocardial contractility. It is apparent from the present investigations that the different effects of these agents on cardiac output are not the result of any dissimilarity in their actions on myocardial contractility, but are probably related to different effects on the peripheral vascular bed. The changes in cardiac output may be explained as follows: norepinephrine augments systemic vascular resistance,[8] which in turn tends to result in reflex bradycardia and diminished cardiac output, despite the increased myocardial contractile force. Epinephrine, on the other hand, tends to diminish peripheral resistance,[9] and its positive chronotropic effect is unopposed by a stimulation of baroceptors. Cardiac output thus rises with increments of myocardial contractile force of a similar magnitude to those produced by norepinephrine. A similarity in the cardiac actions of these catecholamines in man had been previously suggested by the data obtained by Wilber and Brust,[24] which showed that norepinephrine increased cardiac output after atropine or tetraethylammonium bromide had prevented reflex bradycardia.

Although the longer acting sympathomimetic amines, mephentermine and metaraminol, were administered on relatively few occasions in the present study, they always produced increments in contractile force of a magnitude similar to those following norepinephrine, but of longer duration. It appears, therefore, that sympathomimetic amines that increase arterial blood pressure in man may be divided, as in the dog, into 3 classes:[5] Class I amines, such as norepinephrine and epinephrine, increase myocardial contractility and have a short duration of action; Class II amines, such as methoxamine, have little or no effect on myocardial contractility and act longer; Class III amines, mephentermine and metaraminol, increase contractility and have an action of long duration. Additional studies are being conducted with other amines to ascertain whether these agents may be similarly classified.

The strain-gage arch, as a method for measuring myocardial contractile force, was found to be applicable in man as in the experimental animal. No complications arose from its use in the present investigation, and the presence of the arch did not interfere with the surgical procedure. It should be emphasized that in order for the strain-gage arch to measure the direct effects of drugs on the contractile force of the heart, the segment of myocardium between the 2 legs of the strain-gage must be stretched to approximately 50 per cent of its initial length. As Cotten and associates[23, 25, 26] previously demonstrated in the dog, this procedure eliminates significant changes in contractility produced by extracardiac effects of drugs, such as alterations in peripheral resistance, which would modify the end-diastolic fiber length and consequently the force of contraction. Other possible effects of increased systemic vascular resistance on myocardial contractile force measurements were further minimized in this study, since the strain-gage arch was placed on the right ventricle. The augmentation in contractile force produced by norepinephrine and other sympathomimetic amines cannot, therefore, be attributed to increases in peripheral resistance. With the strain-gage arch the effects of at least 2 agents on myocardial contractile force should be compared in the same patient, since it has been demonstrated that considerable variability

exists in the magnitude of the contractile force increments produced by the same agent in different patients. If one agent is considered as the standard of reference, as nonepinephrine was in this study, the effects of all other drugs may be compared with those of the standard and individual responses in various patients can be analyzed.

The results of the present study are important in any consideration of the therapeutic indications for the administration of amines. They emphasize that the cardiovascular actions of these drugs differ strikingly when equipressor doses are given. It is now apparent that although norepinephrine and methoxamine both elevate the blood pressure and diminish the heart rate, these 2 agents should not be considered to be interchangeable, as has previously been suggested.[27, 28] For example, if a patient is hypotensive because of impaired myocardial contractility, as in shock that may accompany myocardial infarction, the administration of an amine with only a pressor effect, such as methoxamine, would appear to be contraindicated. The augmentation of peripheral resistance produced by this amine, in the absence of a direct cardiac action, could result in cardiac dilatation and in pulmonary venous hypertension. Amines such as norepinephrine and metaraminol increase both myocardial contractility and peripheral resistance and would appear to be more suitable in this clinical situation. On the other hand, if a patient is hypotensive primarily because of a fall in peripheral resistance but has no impairment of myocardial contractility, as may occur during spinal anesthesia, methoxamine may be more applicable. These concepts had been presented previously on the basis of extensive animal experimentation[3, 5, 6] and a few preliminary clinical observations.[6] Perhaps because of the mistaken impression that these amines do not have the same actions in animals and man, these principles have not been widely applied in clinical practice. It is hoped that a more rational basis for clinical use has been provided by the present comparative studies of the direct effects of these drugs on the contractility of the human heart.

Summary

The effects of 5 sympathomimetic amines on myocardial contractile force were determined with the Walton-Brodie strain-gage arch in 16 patients undergoing operations for congenital heart disease. Equal doses of norepinephrine and epinephrine produced almost identical increments in myocardial contractile force; equipressor doses of methoxamine resulted in little or no change in the force of contraction. Mephentermine and metaraminol produced increments in myocardial contractile force similar to those following norepinephrine administration but the duration of action was longer. The results of these studies indicate that there are no qualitative differences in the actions of these amines on cardiac contractile force of dog and man and provide a basis for the rational clinical use of these agents.

Acknowledgment

The authors appreciate the cooperation of Drs. N. S. Braunwald and J. W. Gilbert of the National Heart Institute, Clinic of Surgery, and Drs. R. C. Brown, G. R. Christenson, and C. L. Hebert of the Clinical Center Department of Anesthesia.

Summario in Interlingua

Le effectos de 5 aminas sympathomimetic super le fortia del contractilitate myocardial esseva determinate per medio del arco de Walton-Brodie in 16 patientes subjicite a operationes pro congenite morbo cardiac. Doses equal de norepinephrina e de epinephrina produceva quasi identic augmentos in le fortia de contraction del myocardio. Doses equipressori de methoxamina resultava in pauc o nulle alteration del fortia de contraction. Mephentermina e metaraminol produceva augmentos del fortia de contractilitate myocardial simile a illos occurrente post le administration de norepinephrina, sed le duration del effecto esseva plus longe. Le resultatos de iste studios indica que il existe nulle differentias qualitative in le action de iste aminas super le fortia de contraction cardiac in canes o in humanos. Illos provide le base pro le utilisation rational de iste agentes in le practica clinic.

References

1. GARB, S.: Inotropic action of epinephrine, norepinephrine and N-isopropylnorepinephrine on heart muscle. Proc. Soc. Exper. Biol. & Med. **73**: 134, 1950.
2. MELVILLE, K. I., AND LU, F. C.: Effects of ephedrine, phenylephrine, isopropylarterenol, and methoxamine on coronary flow and heart activity as recorded concurrently. Arch. int. Pharmacodyn. **92**: 108, 1952.

3. SARNOFF, S. J., CASE, R. B., BERGLUND, E., AND SARNOFF, L. C.: Ventricular function V: Circulatory effects of aramine. Mechanism of action of "vasopressor" drugs in cardiogenic shock. Circulation **10:** 84, 1954.

4. WELCH, G. H., JR., BRAUNWALD, E., CASE, R. B., AND SARNOFF, S. J.: The effect of mephentermine sulfate on myocardial oxygen consumption, myocardial efficiency and peripheral vascular resistance. Am. J. Med. **24:** 871, 1958.

5. GOLDBERG, L. I., COTTEN, M. DEV., DARBY, T. D., AND HOWELL, E. V.: Comparative heart contractile force effects of equipressor doses of several sympathomimetic amines. J. Pharmacol. & Exper. Therap. **108:** 177, 1952.

6. GAZES, P. C., GOLDBERG, L. I., AND DARBY, T. D.: Heart force effects of sympathomimetic amines as a basis for their use in shock accompanying myocardial infarction. Circulation **6:** 883, 1953.

7. COTTEN, M. DEV., AND PINCUS, S.: Comparative effects of a wide range of doses of l-epinephrine and l-norepinephrine on the contractile force of the heart *in situ*. J. Pharmacol. & Exper. Therap. **114:** 110, 1955.

8. GOLDENBERG, M., PINES, K. L., BALDWIN, E. DEF., GREENE, D. C., AND ROH, C. E.: Hemodynamic response of man to norepinephrine and epinephrine and its relation to the problem of hypertension. Am. J. Med. **5:** 792, 1948.

9. CYVIN, K., JAHREN, G., JORSTAD, J., AND RETTERSTOL, N.: Hemodynamic studies on adrenaline. Acta. med. scandinav. **153:** 67, 1955.

10. BARCROFT, H., AND STARR, I.: Comparison of the actions of adrenaline and noradrenaline on the cardiac output in man. Clin. Sc. **10:** 295, 1951.

11. FOWLER, N. O., WESTCOTT, R. N., SCOTT, R. C., AND MCGUIRE, J.: The effect of norepinephrine upon pulmonary arteriolar resistance in man. J. Clin. Invest. **30:** 517, 1951.

12. BROFMAN, B. L., HELLERSTEIN, H. K., AND CASKEY, W. H.: Mephentermine—an effective pressor amine. Am. Heart J. **44:** 396, 1952.

13. PATEL, D., LANGE, R., AND HECHT, H.: Some evidence for active constriction in the human pulmonary vascular bed. Circulation **18:** 19, 1958.

14. TUCKMAN, J., AND FINNERTY, F. A., JR.: Cardiac index during intravenous levarterenol infusion in man. Circulation Research **7:** 988, 1959.

15. DARBY, T. D., WALTON, R. P., AND GAZES, P. C.: Effects of drugs on ballistocardiographic recordings. Correlation with other cardiovascular measurements in the dog and in man. Am. J. Cardiol. **3:** 668, 1959.

16. TAINTER, M. L., AND LANDS, A. M.: Certain effects of sympathomimetic amines on the heart. New York State J. Med. **53:** 1433, 1953.

17. LEVY, M. N., AND BRIND, S. H.: Influence of l-norepinephrine upon cardiac output in anesthetized dogs. Circulation Research **5:** 85, 1957.

18. AVIADO, D. M.: Cardiovascular effects of some commonly used pressor amines. Anesthesiology **20:** 71, 1959.

19. SELZER, A., AND RYTAND, D. A.: Use of drugs in shock accompanying myocardial infarction. J.A.M.A. **168.** 762, 1958.

20. BONIFACE, K. J., BRODIE, O. J., AND WALTON, R. P.: Resistance strain gauge arches for direct measurement of heart contractile force in animals. Proc. Soc. Exper. Biol. & Med. **84** 263, 1953.

21. DARBY, T. D., PARKER, E. F., LEE, W. H., AND ASHMORE, J. D.: The influence of cardiopulmonary bypass with cardiac arrest and right ventriculotomy on myocardial contractile force. Ann. Surg. **147:** 596, 1958.

22. BLOODWELL, R. D., GOLDBERG, L. I., BRAUNWALD, E., GILBERT, J. W., ROSS, J., JR., AND MORROW, A. G.: Myocardial contractility in man: the acute effects of digitalis, sympathomimetic amines and anoxic cardiac arrest. Surg. Forum. In press.

23. COTTEN, M. DEV.: Circulatory changes affecting measurement of heart force *in situ* with strain gauge arches. Am. J. Physiol. **174:** 365, 1953.

24. WILBER, J. A., AND BRUST, A. A.: The circulatory and metabolic effects in man of histamine, mecholyl, tetraethylammonium and atropine in the presence of circulating epinephrine and norepinephrine. J. Clin. Invest. **37:** 476, 1958.

25. COTTEN, M. DEV., AND BAY, E.: Direct measurement of changes in cardiac contractile force. Relationship of such measurements to stroke work, isometric pressure gradient and other parameters of cardiac function. Am. J. Physiol. **187:** 122, 1956.

26. —, AND MALING, H. M.: Relationships among stroke work, contractile force and fiber length during changes in ventricular function. Am. J. Physiol. **189:** 580, 1957.

27. GRIFFITH, G. C., WALLACE, W. B., COCHRAN, B., NERLICH, W. E., AND FRASHER, W. G.: The treatment of shock associated with myocardial infarction. Circulation **9:** 527, 1954.

28. GOODMAN, L. S., AND GILMAN, A.: The pharmacological basis of therapeutics. Ed. 2. New York, Macmillan, 1956, p. 531.

Correlation of the Roentgen Appearance of the Thoracic Aorta in Life with the Degree of Stenosing Arteriosclerosis of the Coronary Arteries at Necropsy

By IRVING M. LIEBOW, M.D., ROBERT R. OSEASOHN, M.D., GEORGE F. BADGER, M.D., AND BENJAMIN KAUFMAN, M.D.

IN THE absence of angina pectoris or a history of myocardial infarction the diagnosis of arteriosclerotic heart disease (coronary heart disease, coronary arteriosclerotic heart disease, coronary artery heart disease) is, in clinical practice, one of exclusion. The diagnosis is made in a patient in the "proper" age group who has symptoms or signs of heart disease and none of the other obvious causes (valvular disease, hypertension, hyperthyroidism, congenital heart disease, etc.).

The New York Heart Association has attempted to place the diagnosis of arteriosclerotic heart disease on a more objective basis and has stated[1] in part, ". . . the etiological diagnosis, 'Arteriosclerosis,' should be limited to those cases of heart disease showing definite evidence of arteriosclerosis of the coronary arteries or the arch of the aorta." Definite evidence of arteriosclerosis of the coronary arteries would, of course, establish the etiologic diagnosis by definition. The reason for accepting evidence of arteriosclerosis of the arch of the aorta as a criterion for the etiologic diagnosis is not so clear, however, because such a criterion implies that there is a positive correlation between the presence of arteriosclerosis of the aorta and stenosing arteriosclerosis of the coronary arteries. A survey of the literature discloses little information and no unanimity of opinion on this point. Several authors[2-5] deny the correlation but give no references. Willius, Smith, and Sprague,[6] in a necropsy study of coronary and aortic sclerosis, found "fairly close parallelism between the degree of coronary and of aortic sclerosis . . . [but] much discrepancy in many instances." The proportion of cases in which discrepancy occurred was not given. Similarly, Higginson and Pepler,[7] in a study of atherosclerosis in the South African Bantu, stated, "These cases (with marked atherosclerosis of the coronary arteries) are frequently but not invariably associated with well-marked aortic disease." The precise degree of association, or lack of it, was not given. Tejada and Gore,[8] in a necropsy study of the aorta alone, showed a greater prevalence of atherosclerosis in natives of New Orleans than in people of the low-income group of Guatemala and added, "It is pertinent to note that paralleling the difference in atherosclerosis, over age 40 in the two localities, there were 51 cases of myocardial infarction in New Orleans from a total of 316 cases and only one in the Guatemalan group of 234 cases . . . ." The authors obviously imply a correlation between coronary and aortic atherosclerosis, but no actual study of the coronary arteries was presented in their paper.

In view of this lack of specific information we decided to determine if the diagnosis can be based on the presence of abnormality of the aorta and specifically on abnormality of the aorta that can be detected in the living patient. The finding of symptoms or abnormal physical signs indicating arteriosclerosis of the arch of the aorta, as required by the "Criteria,"[1] is uncommon. It would, in fact, be limited to the relatively rare case of aneurysm and to the occasional case of marked

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This study was part of the Diabetes Research Program of Western Reserve University and was supported in part by The Foundation for the Study of Diabetes and Related Metabolic Disorders and by U. S. Public Health Service grant number A-1317 (C).

elongation with palpable pulsation in the suprasternal notch. Clinically, the more common way of noting abnormality of the aorta is by means of the standard 6-foot roentgenogram of the chest. It was decided, therefore, to compare the appearance of the thoracic aorta in life as seen on the x-ray film with the condition of the coronary arteries as noted at necropsy.

Method

A review was made of the autopsy protocols at the Institute of Pathology, Western Reserve University, beginning with those of January 1, 1956, and ending in November 1956. The beginning date was chosen because at that time standard printed diagrams for description of each organ system, including heart and coronary arteries, were introduced as a routine part of the protocols. All cases were listed except those autopsies that did not include examination of the heart, those in which the degree of coronary arteriosclerosis was not mentioned, autopsies on patients under 15 years of age, and cases showing syphilis of the aorta. The degree of stenosing arteriosclerosis of the coronary arteries and their main stem branches was recorded. The terms used to describe coronary arteriosclerosis were relatively few in number and easily fell into 5 groups of increasing degree of stenosis: (1) "normal" or "none," (2) "mild," "slight," or "minimal," (3) "moderate," (4) "severe" or "marked," (5) "complete" (with or without recanalization). The most marked degree of arteriosclerosis found in the coronary artery system was used. The protocols in some instances did not detail in which particular coronary artery or main stem the described degree of arteriosclerosis was found, so that in the final analysis the degree of arteriosclerosis used was the most severe found anywhere in a main coronary artery or one of the main stem branches. For tabulation "normal" and "none" were called "none," "mild," "slight," "minimal" was called "slight," and "severe," "marked," and "complete" were called "severe."

The roentgenograms for the cases listed from the autopsy protocols were drawn from the files. The last posteroanterior roentgenogram made during the hospitalization that terminated in necropsy was used, providing the examination was made within 90 days of death (with the day of death being considered as the ninetieth day), and providing a satisfactory view of the aorta was afforded. Cases that did not meet these requirements were dropped from the study. All remaining cases were retained as the final study material; they totaled 137. Consecutive autopsy protocols of 463 patients were reviewed initially. Of these, 128 were omitted because the patients were under age 15. Of the remaining 335, 108 could not be used because no chest film had been made within 90 days of death. Of the 227 remaining cases 90 were omitted for the following reasons: there had been no examination of the heart at autopsy; syphilis of the aorta had been found at necropsy; the degree of coronary arteriosclerosis was not mentioned in the autopsy protocol; the roentgenogram did not give a satisfactory view of the aorta; or the roentgenogram was missing from the files.

A review of the original x-ray reports showed that the terms used to describe abnormalities of the aorta were few: "calcification," "tortuosity," "widening," "dilatation," and "prominent knob." A pilot study showed that when films were reread without specific questions asked but simply with attention focused on the aorta, not only were observations made that were different from the original, but a greater number of observations were made. For this reason the original interpretations were ignored and all the films were reread by one individual, a trained roentgenologist. The re-interpretation was made by means of a "Yes-No-Maybe-Unable to interpret" check-off list, which specifically asked the examiner to state whether or not calcification, tortuosity, elongation, widening, dilatation, or prominence of the knob of the aorta was present.

These terms really describe only 2 types of abnormality of the aorta, disease of the intima and disease of the media. Calcification of the crescentic type seen in the knob and the linear type seen in the descending portion of the thoracic aorta is indicative of intimal atherosclerosis.[9] All the other terms are indicative of the increase in caliber or length of the aorta, or both, resulting from medial sclerosis.[10] Two sets of analyses were made, therefore: (1) an analysis to see if there was any correlation between calcification of the aorta (intimal disease) as noted in the chest film of each patient and the degree of stenosing coronary arteriosclerosis of the same patient as noted at necropsy; (2) a similar analysis for enlargement (medial disease) of the aorta.

Results

Calcification (Intimal Disease) of the Aorta

Table 1 shows the degree of atherosclerosis of the coronary arteries found at necropsy in patients with and without calcification of the thoracic aorta as seen in a posteroanterior chest film.

The totals show that when calcification was present 71 per cent of the patients had moderate or severe coronary atherosclerosis, and when calcification was absent 58 per cent had moderate or severe coronary atherosclerosis.

Table 1

Prevalence of Various Degrees of Coronary Atherosclerosis in Patients with and without Aortic Calcification Noted Roentgenographically, by Age Groups

Age Group	Aortic calcification present				Aortic calcification absent			
	Degree of coronary atherosclerosis at necropsy			% Moderate or severe	Degree of coronary atherosclerosis at necropsy			% Moderate or severe
	None or slight	Moderate or severe	Total no.		None or slight	Moderate or severe	Total no.	
20-49	8	3	11	27	9	4	13	31
50-59	4	6	10	60	8	12	20	60
60+	7	37	44	84	8	19	27	70
Total	19	46	65	71	25	35	60	58

Table 2

Prevalence of Various Degrees of Coronary Atherosclerosis in Patients with and without Aortic Englargement Noted Roentgenographically, by Age Groups

Age Group	Aortic enlargement present				No enlargement present			
	Degree of coronary atherosclerosis at necropsy			% Moderate or severe	Degree of coronary atherosclerosis at necropsy			% Moderate or severe
	None or slight	Moderate or severe	Total no.		None or slight	Moderate or severe	Total no.	
20-49	5	4	9	44	10	3	13	23
50-59	10	13	23	57	2	3	5	60
60+	13	54	67	81	2	3	5	60
Total	28	71	99	72	14	9	23	39

This difference is more apparent than real, however, and is largely due to the fact that those with calcification are really an older group than those without calcification. When the figures were examined age-by-age, no difference was seen under 60 years of age, and only a minor and statistically insignificant difference (84 versus 70 per cent) in the older age group.

Enlargement (Medial Disease) of the Aorta

Table 2 shows the degree of atherosclerosis of the coronary arteries found at necropsy in patients with and without enlargement of the thoracic aorta as seen in a posteroanterior chest film. Again, the difference in the prevalence of moderate or severe atherosclerosis in the 2 groups is largely due to the age distribution. Most of those with aortic enlargement were over age 60, while most of those without enlargement were under age 50. Actually there were too few patients without enlargement to warrant any conclusion about a relationship between enlargement of the aorta and coronary atherosclerosis. From the point of view of clinical diagnosis, however, it is clear that very few older patients showed normal aortic outlines, that coronary atherosclerosis was present in the majority of patients over age 50 regardless of roentgenographic evidence of aortic enlargement, and that the latter is of little value in predicting the presence of coronary atherosclerosis.

Discussion and Conclusion

The "Nomenclature and Criteria . . ." of the New York Heart Association states in part that the diagnosis of coronary artery heart disease rests upon the finding of abnormal physical signs indicating arteriosclerosis of the aorta. This implies that there is a positive correlation between the presence of arteriosclerosis of the aorta and stenosing arteriosclerosis of the coronary arteries. To test the validity of this assumption a comparison was made between the appearance of the thoracic aorta as seen on an x-ray film shortly before death with the degree of stenosing coronary arteriosclerosis noted at necropsy.

The results indicate that roentgenographic evidence of arteriosclerosis of the thoracic

aorta, whether calcification (intimal atherosclerosis) or enlargement (medial arteriosclerosis), does not constitute an accurate basis for the diagnosis of coronary arteriosclerosis. Indeed, more accurate information regarding the state of the coronary arteries is obtained by simply noting the patient's age.

It is therefore concluded that arteriosclerosis of the aorta noted roentgenographically should not be a criterion for the etiologic diagnosis of coronary artery heart disease.

Acknowledgment

The authors are most grateful to Dr. Alan Moritz for his cooperation in the use of the protocols at the Institute of Pathology, Western Reserve University.

Summario in Interlingua

Le "Nomenclatura e Criterios pro le Diagnose de Morbos del Corde e del Vasos Sanguinee" ("Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels") del Association Cardiologic de New York assere in parte que le diagnose de morbo cardiac del arteria coronari depende del constatation de anormal signos physic que indica arteriosclerosis del aorta. Isto presuppone que il existe un correlation positive inter le presentia de arteriosclerosis del aorta e arteriosclerosis stenotisante del arterias coronari. Pro testar le validitate de iste supposition, un comparation esseva facite inter le apparentia del aorta thoracic in roentgenographias obtenite brevemente ante morte e le grado de stenotisante arteriosclerosis coronari notate al necropsia.

Le resultatos indica que le evidentia roentgenographic de arteriosclerosis del aorta thoracic—si illo consiste de calcification (atherosclerosis intimal) o de allargamento (arteriosclerosis medial)—non constitue un accurate base pro le diagnose de arteriosclerosis coronari. De facto, plus accurate information con respecto al stato del arterias coronari pote esser obtenite per simplemente notar le etate del patiente.

Es concludite, per consequente, que arteriosclerosis del aorta secundo constatationes roentgenographic non debe esser reguardate como un criterio in le diagnose etiologic de morbo cardiac de arteria coronari.

References

1. Criteria Committee of the New York Heart Association Inc.: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels. Ed. 5. New York Heart Association, Inc., 1955, p. 16, paragraph 1.
2. Von Glahn, W. C.: The pathology of the coronary arteries. *In* Diseases of the Coronary Arteries and Cardiac Pain. Edited by Robert L. Levy. New York, The MacMillan Co., 1938, p. 141.
3. Friedberg, C. K.: Diseases of the Heart. Ed. 2. Philadelphia, W. B. Saunders Co., 1956, p. 435.
4. Bell, E. T.: Textbook of Pathology. Ed. 8. Philadelphia, Lea & Febiger, 1956, p. 717.
5. Karsner, H. T.: Human Pathology. Ed. 4. Philadelphia, J. P. Lippincott Company, 1935, p. 474.
6. Willius, F. A., Smith, H. L., and Sprague, P. H.: Study of coronary and aortic sclerosis: Incidence and degree in 5,060 consecutive postmortem examinations. Proc. Staff Meet., Mayo Clin. 8: 140, 1933.
7. Higginson, J., and Pepler, W. J.: Atherosclerosis in the South African Bantu. J. Clin. Invest. 33: 1366, 1954.
8. Tejada, C., and Gore, I.: Comparison of atherosclerosis in Guatemala City and New Orleans. Am. J. Path. 33: 887, 1957.
9. Hyman, J. B., and Epstein, F. H.: A study of the correlation between roentgenographic and post-mortem calcification of the aorta. Am. Heart J. 48: 540, 1954.
10. Boyd, W.: Textbook of Pathology, Ed. 6. Philadelphia, Lea & Febiger, 1953, p. 357.

An Index for the Evaluation of Arteriosclerotic Lesions in the Abdominal Aorta

A Report by the Committee on Lesions of the American Society for the Study of Arteriosclerosis*

By Russell L. Holman, M.D., Chairman†, B. W. Brown, Ph.D., Ira Gore, M.D., Gardner C. McMillan, M.D., James C. Paterson, M.D., O. J. Pollak, M.D., Ph.D., James C. Roberts, Jr., M.D., and Robert W. Wissler, M.D.

THE NEED for uniform and reproducible methods to grade the lesions of arteriosclerosis‡ has long been recognized.[1-43]

In this report are presented *pro tempore* the results and recommendations of the Committee on Lesions of the American Society for the Study of Arteriosclerosis based on studies of the abdominal aorta of man during the past 3 years. The methods may prove useful in other parts of the arterial system and thus facilitate basic studies on arteriosclerosis in man and in animals.

It should be emphasized that this approach to the quantitative evaluation of aortic lesions does not preclude combining it with other methods of measuring the degree of disease in a given vessel. Physical or chemical measurements of many types can be made on the same vessels.

Methods

(1) Anatomic material was preserved for repeated studies. Opened, flattened, formalin-fixed segments of the aorta preserved in plastic bags with coded labels proved convenient for this purpose. Repeated observations using a variety of criteria for assessment were made on the material by 7 pathologists and their associates. The observations reported here were all of a simple type that could be made by inspection alone or inspection aided by some simple measuring device such as a centimeter scale.

(2) A biostatistician served as referee and coordinator of the studies.

(3) The systems of grading that were studied took cognizance of the quantitative and qualitative aspects of the lesions.

(a) *Quantitative estimates* were expressed as the percentage of intimal surface area that showed arteriosclerosis.

(b) *Qualitative features* of the individual lesions usually allowed them to be classified on inspection as:

(1) Fatty lesions (fatty streaks or predominantly fatty plaques).

(2) Fibrous plaques or diffuse thickening of the intima.

(3) Complicated lesions (old or recent hemorrhage, ulceration, thrombosis, calcification).

These three qualitative estimates were then expressed quantitatively as a percentage of the abnormal surface area and, consequently, they always totaled 100 per cent.

When fatty deposits were difficult to visualize, it was found useful to stain the whole vessel with a fat-soluble dye such as Sudan IV.

Calcification, both intimal and medial, was assessed separately but it was found in practice that it could ordinarily be included in the percentage of qualitative change recorded as complicated lesion. In certain cases, calcification could be felt in the gross specimen lying beneath an intact intimal surface in which there were no obvious complications. Its presence was confirmed by histologic and radiologic studies. The appropriate assessment of these lesions remained unresolved, but they did not seriously interfere with the use of the simple methods outlined above. Table 1 shows the form used in recording the data.

Supported in part by a grant (H-3165) from the National Heart Institute, U. S. Public Health Service.

Published with the approval of the Executive Committee of the Council on Arteriosclerosis and the Central Committee of the American Heart Association.

*Now Council on Arteriosclerosis of the American Heart Association.

†Deceased.

‡For the purposes of this study arteriosclerosis has been used to indicate the involvement of the *intima* which can be seen and evaluated grossly. The components of the lesions which have been included are (1) fatty streaks and plaques; (2) fibrotic intimal thickening; and (3) complicated lesions which include hemorrhage, ulceration, thrombosis, and calcification.

Table 1

Abdominal Aorta Grading Sheet. Committee on Lesions, Council on Arteriosclerosis, American Heart Association (American Society for the Study of Arteriosclerosis)

Code number	A:/Per cent of intimal area covered by any lesion	B:/per cent of A as			C:/per cent of complication (B_3.) as				Atherosclerosis index = $\frac{1}{2}A + \frac{1}{4}B_2 + \frac{1}{2}B_3$
		1:/Fat	2:/Fibrosis	3:/Complication	Hemorrhage	Ulcer	Thrombus	Calcium	

(4) *Assessment by ranking:* In addition, groups of abdominal aortas were arranged or ranked to form series in which each specimen was judged to be more severely affected with arteriosclerosis than the preceding one.

(5) *Topographical features* of the lesions were kept relatively constant by studying only the abdominal aorta from the inferior margin of the celiac axis to a line drawn across the top of the point of bifurcation into the iliac arteries. No attempt has been made to describe the topographical features of lesions in this report. They vary in different anatomical areas.

Materials

A. Twenty-six aortas were chosen from 120 aortas submitted (20 each) by the members of the Committee from 6 different cities of North America. These were selected by the biostatistician with assistance from a pathologist who had experience with arteriosclerosis but was not otherwise active in the present study. The specimens were chosen to provide a series that would encompass the gamut of quantitative and qualitative changes encountered in aortas in North America. After each member of the Committee had graded the quantitative and qualitative aspects of the lesions he was requested to arrange or rank on a subsequent day the 26 specimens in what he judged to be the order of severity of involvement by arteriosclerosis. The specimens were placed in random order by the biostatistician after each ranking. This group of specimens was again graded and ranked by the same observers in another city approximately 1 year later.

B. Twenty-five human abdominal aortas were collected consecutively on the Louisiana State University Service at Charity Hospital, New Orleans. This group was graded and ranked by each member of the Committee.

C. Thirty aortas from the University of Chicago Clinics were selected to span the range of intimal disease. This group was also graded and ranked by each member of the Committee.

The aortas in groups B and C were also ranked by a resident in pathology and a junior member of a department of pathology who had no previous contact with the work of the Committee.

Results

The data for each of the 3 groups of aortas were analyzed separately. The rankings given independently by the several judges who arranged the aortas in order of their severity of involvement by arteriosclerosis were examined to see if the agreement between the six judges

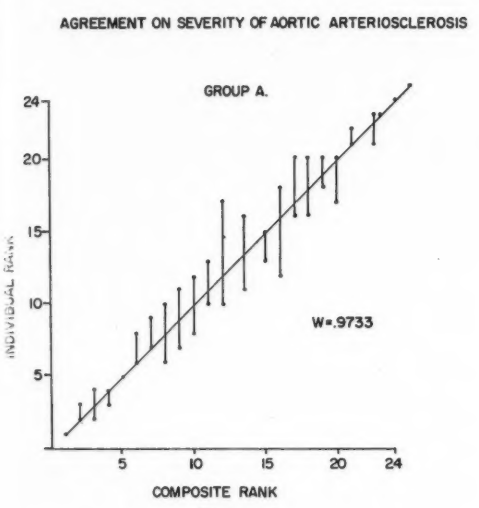

Figure 1

Severity rank data for aortas of group A.

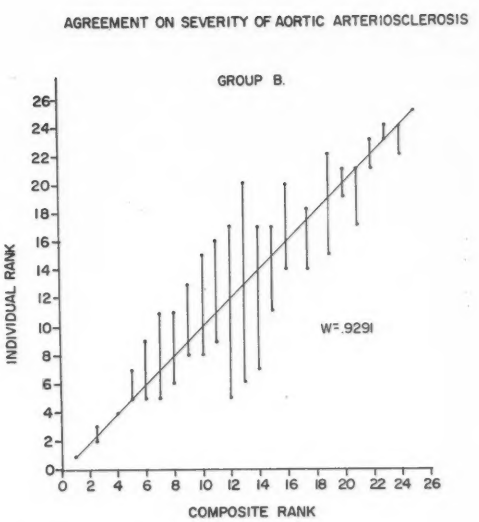

Figure 2

Severity rank data for aortas of group B.

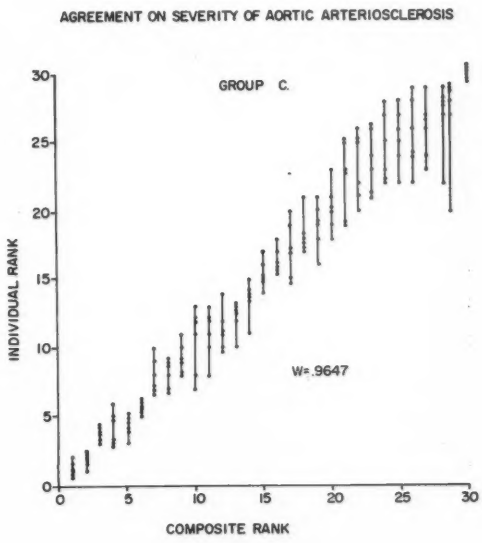

Figure 3

Severity rank data for aortas of group C.

was good enough to justify an index related to the severity of arteriosclerosis. The severity rank data are presented in figures 1, 2, and 3. The coefficients of concordance are high: 0.97, 0.93, and 0.96 for groups A, B, and C respectively.

The degree of subjectivity of the visual estimates of percentage of intimal surface involved by lesions was examined. Figures 4, 5, and 6 show the data for estimation of over-all area covered with arteriosclerotic lesions (P_T). For aortas approximately 50 per cent involved the judges agreed to within ± 20 per cent. In an occasional aorta (2 of 26) the interpretation of large areas of diffuse fibrous intimal thickening caused important disagreement. In general, the agreement was better for the more diseased and for less diseased aortas. There was less agreement among the judges in estimating the percentages of the different types of lesions. For example, the visual estimates for fibrous plaques by the seven judges varied from 10 to 60 per cent on an occasional specimen; and this magnitude of variation could also be found in the visual estimates for complicated lesions. This degree of variation, however, was the exception rather than the rule; and no consistent variation—or "correction factor"—for any 1 of the 7 judges emerged from a careful study of all the recorded data.

The index constructed from the quantitative estimates of the percentage area involved by the several types of lesions is of the form

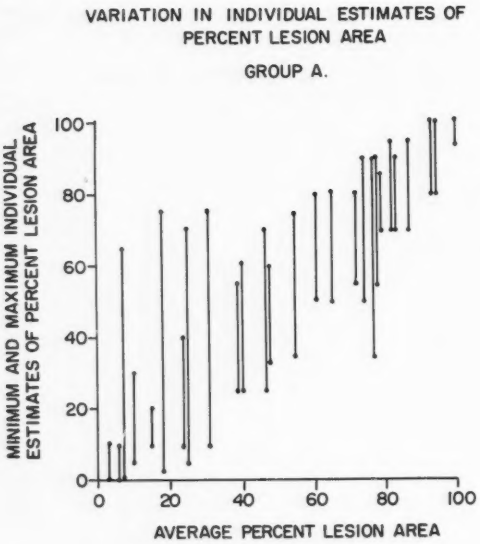

Figure 4

Estimation of total diseased intimal surface of aortas of group A.

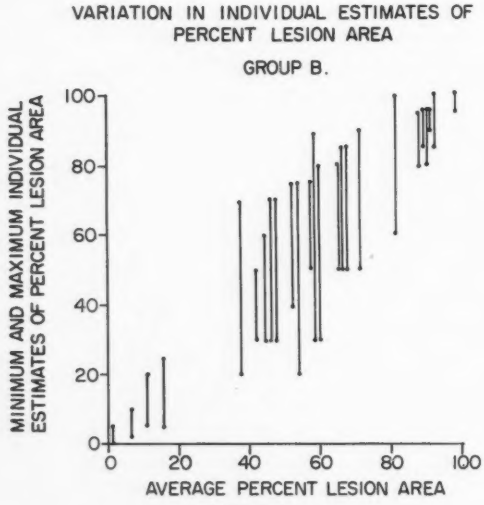

Figure 5

Estimation of total diseased intimal surface of aortas of group B.

$I = B_T P_T + B_F P_F + B_C P_C$. P_T is the quantitative estimate of the per cent of total area (T) covered with lesions; P_F and P_C the per cent lesion area covered with fibrous plaques (F)

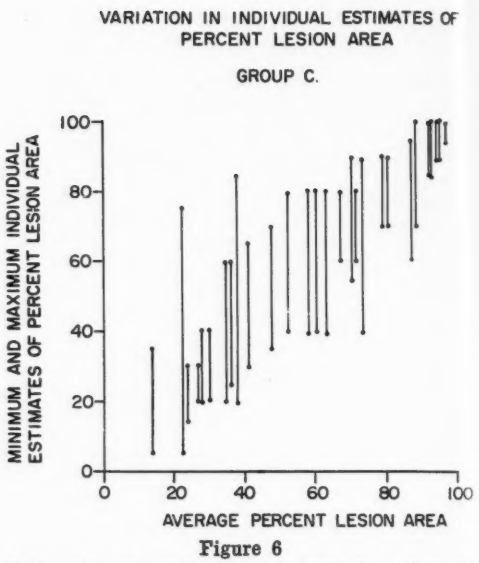

Figure 6

Estimation of total diseased intimal surface of aortas of group C.

and complicated lesions (C), respectively. The constants, B, are weights determined so as to obtain maximum agreement between the index values and the severity rankings within a group of aortas.

The rankings were transformed to expected values of the order statistics for a normal distribution with mean 50 and standard deviation 20. The transformed values and the value of P_T, P_F, and P_C were used to obtain least-squares estimates of B_T, B_F, and B_C.

It should be noted that, since the sum of the percentages of intimal surface affected by the three types of lesions studied (fatty, fibrous, and complicated) must equal 100 per cent of the total area involved by lesions, only 2 of the 3 types of lesions are represented directly in the formula, the third type (fatty lesions) being represented indirectly.

The statistically determined weights, B, were calculated separately for each of the 3 groups. The results were:

Group A: $I = .51P_T + .15P_F + .57P_C$

Group B: $I = .45P_T + .27P_F + .64P_C$

Group C: $I = .54P_T + .26P_F + .47P_C$

On the basis of the results the index for the

evaluation of arteriosclerotic lesions, $I = 1/2P_T + 1/4P_F + 1/2P_C$, is proposed for the human abdominal aorta. While it may be more generally applicable, it should be noted that it has been devised by use of specimens from the general autopsy population in North America. The weighting coefficients are compromise values based on the least-squares solutions; they are easy to remember and use; and they make the maximum value of the index exactly 100.

Comment

The index does not have etiologic or pathogenetic implications. It is based on the simple, visual inspection of arteriosclerotic lesions carefully observed and recorded by pathologists. The study has elicited a high degree of concordance among the several observers. Nevertheless, the method is subjective and, consequently, it can be distorted by inexperience, unusual criteria, or carelessness. On the other hand, preliminary study indicates that very little experience with the pleomorphism of arteriosclerotic lesions is required before adequate and reproducible assessment is possible. The method is rapid and requires no special equipment, although it may be useful to stain specimens from young individuals and from animals with a fat-soluble dye. It is capable of providing a relatively uniform evaluation of arteriosclerotic lesions within the same laboratory or between different laboratories. Since the index is related to the severity of arteriosclerosis as ascertained by ranking procedures, it will predict the place of a specimen in a series ranked in severity.

Summary

An index for the evaluation of arteriosclerotic lesions based on visual observation of selected and unselected specimens of the abdominal aorta was derived from a statistical analysis of simple grading and ranking studies.

This index, $I = 1/2P_T + 1/4P_F + 1/2P_C$, takes cognizance of most of the grossly visible quantitative and qualitative features of human arteriosclerotic lesions. In it P_T, P_F, and P_C are the quantitative estimates of the per cent of total area diseased (T) and the per cent lesion area with fibrous plaques (F) and complicated lesions (C), respectively. The index is subjective but relatively reproducible by the same or different observers. It does not carry any implications of etiology or pathogenesis. The work of the Committee is continuing, and it is hoped that indices based on such methods may prove useful when applied to other parts of the arterial system or in studying several parts simultaneously, thus facilitating basic studies on arteriosclerosis both in man and in animals.

Acknowledgment

Assistance from many consultants is gratefully acknowledged.

Summario in Interlingua

Un indice pro le evalutation de lesiones arteriosclerotic, basate super le observation visual de seligite e non-seligite specimens de aorta abdominal esseva derivate ab le analyse statistic de simple studios de marcation e seriation relative.

Iste indice, $I=\frac{1}{2}P_T + \frac{1}{4}P_F + \frac{1}{2}P_C$, prende in consideration le majoritate del grossiermente visibile characteristicas quantitative e qualitative de lesiones arteriosclerotic human. In illo, P_T, P_F, e P_C es estimationes quantitative del procentage de terreno morbide total (T) e del procentages del terreno morbide que exhibi placas fibrose (F) e lesiones complicate (C), respectivemente. Le indice es subjective, sed illo es relativemente reproducibile per le mesme o per un altere observator. Le indice ha nihil a signalar ab le puncto de vista del etiologia o del pathogenese. Le labores del committee va continuar, e le spero es exprimite que indices de iste genere va esser utile quando illos es applicate a altere partes del systema arterial o quando plure partes es studiate simultaneemente. Isto renderes plus facile le studio fundamental de arteriosclerosis in humanos e animales.

References

1. Ackerman, R. F., Dry, T. J., and Edwards, J. E.: Relationship of various factors to the degree of coronary atherosclerosis in women. Circulation 1: 1345, 1950.
2. Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Studies of the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to pathologic findings. Am. Heart J. 19: 1, 1940.
3. Buck, R. C., and Rossiter, R.: Lipids of normal and atherosclerotic aortas—a chemical study. A.M.A. Arch. Path. 51: 224, 1951.
4. Cook, D. L., et al: The effects of cholesterol dos-

age, cortisone, and DCA on total serum cholesterol lipoproteins, and atherosclerosis in the rabbit. J. Exper. Med. 96: 27, 1952.

5. DAVIS, D., AND KLAINER, M. J.: Studies in hypertensive heart disease. I. The incidence of coronary atherosclerosis in cases of essential hypertension. Am. Heart J. 19: 185, 1939.
6. DAY, A. J., AND WILKINSON, G. K.: Severity of atherosclerosis in rabbits in relation to serum lipids and to aorta cholesterol content. Austral. J. Exper. Biol. 34: 423, 1956.
7. DOCK, W.: The capacity of the coronary bed in cardiac hypertrophy: J. Exper. Med. 74: 177, 1941.
8. FABER, M., AND LUND, F.: Human aorta: The influence of obesity on development of arteriosclerosis in the human aorta. Arch. Path. 48: 351, 1949.
9. —: The cholesterol content of the human aorta in relation to the serum cholesterol concentration. Acta. med. scandinav. 125: 418, 1946.
10. GORE, I., AND TEJADA, C.: The quantitative appraisal of atherosclerosis. Am. J. Path. 33: 875, 1957.
11. HASS, G. H.: Elastic tissue. II. A study of the elasticity and tensile strength of elastic tissue isolated from the human aorta. Arch. Path. 34: 971, 1942.
12. HOLMAN, R. L., MCGILL, H. C., JR., STRONG, J. P., AND GEER, J. C.: The natural history of atherosclerosis: The early aortic lesions as seen in New Orleans in the middle of the 20th century. Am. J. Path. 34: 209, 1958.
13. —, —, —, AND —: Techniques for studying atherosclerotic lesions. Lab. Invest. 7: 42, 1958.
14. LANDE, K. E., AND SPERRY, W. M.: Human atherosclerosis in relation to the cholesterol content of the blood serum. A.M.A. Arch. Path. 22: 301, 1936.
15. MALISOFF, W. M.: Prevention of atherosclerosis in rabbits. I. Administration of potassium thiocyanate. Proc. Soc. Exper. Biol. & Med. 35: 356, 1936.
16. MCARTHUR, C. S.: The acetone-soluble lipid of the atheromatous aorta. Biochem. J. 36: 559, 1942.
17. MEEKER, D., AND JOBLING, J. A.: A chemical study of atherosclerotic lesions in the human aorta. Arch. Path. 18: 473, 1934.
18. NICHOLS, C. W., JR., et al: Does the ingestion of alcohol influence the development of arteriosclerosis in fowls? J. Exper. Med. 103: 456, 1956.
19. O'NEAL, R. M., AND THOMAS, W. A.: The role of pulmonary hypertension and thromboembolism in the production of pulmonary arteriosclerosis. Circulation 12: 370, 1955.
20. PATERSON, J. C., CORNISH, B. R., AND ARMSTRONG, E. C.: The serum lipids in human atherosclerosis—an interim report. Circulation 13: 224, 1956.
21. PICK, R., STAMLER, J., RODBARD, S., AND KATZ, L. N.: The inhibition of coronary atherosclerosis by estrogens in cholesterol-fed chicks. Circulation 6: 276, 1952.
22. ROBERTS, J. C., MOSES, C., AND WILKINS, R. H.: Autopsy studies in atherosclerosis. I. The distribution and severity of atherosclerosis in patients dying without morphologic evidence of arteriosclerotic catastrophe. Circulation 20: 511, 1959.
23. ROSENTHAL, S. R.: Studies in atherosclerosis: Chemical, experimental and morphologic. I and II. Roles of cholesterol metabolism, blood pressure and structure of the aorta: The fat angle of the aorta (F.A.A.), and the infiltration expression theory of lipid deposit. A.M.A. Arch. Path. 18: 473, 1934.
24. SAPHIR, O., AND GORE, I.: Evidence for an inflammatory basis for coronary arteriosclerosis in the young. Arch. Path. 49: 418, 1950.
25. SAPPINGTON, S. W., AND HORNEFF, J. A.: Tibial artery changes in comparison with those of radial and coronary arteries. Am. J. M. Sc. 201: 862, 1941.
26. SPAIN, D. M., BRADESS, V. A., AND HUSS, G.: Observations on atherosclerosis in the coronary arteries in males under the age of 46: A necropsy study with special reference to somatotypes. Ann. Int. Med. 38: 254, 1953.
27. STEARNS, S., SCHLESINGER, M. J., AND RUDY, A.: Incidence and clinical significance of coronary artery disease in diabetes mellitus. Arch. Int. Med. 80: 463, 1947.
28. STRONG, J. P., MCGILL, H. C., JR., TEJADA, C., AND HOLMAN, R. L.: The natural history of atherosclerosis: Comparison of early aortic lesions in New Orleans, Guatemala and Costa Rica. Am. J. Path. 34: 731, 1958.
29. TEJADA, C., AND GORE, I.: Comparison of atherosclerosis in Guatemala City and New Orleans. Am. J. Path. 33: 887, 1957.
30. —, —, STRONG, J. P., AND MCGILL, H. C., JR.: Comparative severity of atherosclerosis in Costa Rica, in Guatemala, and New Orleans. Circulation 18: 92, 1958.
31. THOMAS, W. A., O'NEAL, R. M., AND LEE, K. T.: Experimental pulmonary hypertension and arteriosclerosis. A.M.A. Arch. Path. 62: 56, 1956.
32. TURNER, K. B.: Studies on the prevention of cholesterol atherosclerosis in rabbits. J. Exper. Med. 58: 115, 1933.
33. WARTMAN, W. B., AND HELLERSTEIN, H. K.: The incidence of heart disease in 2000 consecutive autopsies. Ann. Int. Med. 82: 41, 1948.

34. WEINHOUSE, S., AND HIRSCH, E. F.: Atherosclerosis. II. The lipids of the serum and tissues in experimental atherosclerosis of rabbits. A.M.A. Arch. Path. 30: 856, 1940.
35. —, AND —: Chemistry of atherosclerosis: Lipid and calcium content of the intima and of the media of the aorta with and without atherosclerosis. A.M.A. Arch. Path. 29: 31, 1940.
36. WHITE, N. K., EDWARDS, J. E., AND DRY, T. J.: Relationship of degree of coronary atherosclerosis with age in men. Circulation 1: 645, 1950.
37. WILENS, S. L.: The post mortem elasticity of the adult aorta. Am. J. Path. 13: 811, 1937.
38. —: The resorption of arterial atheromatous deposits in wasting disease. Am. J. Path. 23: 793, 1947.
39. WILLIUS, F. A., SMITH, H. L., AND SPRAGUE, P. H.: A study of coronary and aorta sclerosis incidence and degree in 5060 consecutive post mortem examinations. Proc. Staff Meet., Mayo Clin. 8: 140, 1933.
40. World Health Organization Technical Report Series, No. 143, 1958: Classification of atherosclerotic Lesions.
41. WUEST, J. H., JR., DRY, T. J., AND EDWARDS, J. E.: The degree of coronary atherosclerosis in bilaterally oophorectomized women. Circulation 7: 801, 1953.
42. YATER, W. M., TRAUM, A. H., BROWN, W. G., FITZGERALD, R. P., GEISLER, M. A., AND WILCOX, B. B.: Coronary artery disease in men eighteen to thirty-nine years of age. Am. Heart J. 36: 334, 1948.
43. ZEEK, P. M.: Chemical analysis of atherosclerotic lesions in human aorta. Am. J. Path. 12: 115, 1936.

To such it might, perhaps, be a sufficiently philosophical answer to reply, that an improved knowledge of the nature and causes of a disease, must alone necessarily lead to an improvement in the treatment; and that therapeutic weapons are dangerous when wielded in the dark.—J. HOPE, M.D. *Diseases of the Heart and Great Vessels.* London, William Kidd, 1832, p. 19.

The Effects of Specific Gravity upon the Distribution of Intravascular Contrast Agents

By CHARLES T. DOTTER, M.D., WILLIAM VEATCH, B.S., DAVID WISHART, B.A., AND PAMELA DOTTER, R.N.

*Universally, all bodies around the earth gravitate toward it.**

NEWTON'S 1687 hypothesis applies equally to apples, astronauts, and angiography. As contemporary workers have pointed out,[1-3] contrast substances possess specific gravities different from that of blood. Ordinarily, contrast visualization of the cardiovascular system is carried out with the patient in a horizontal position and the x-ray beam oriented vertically. As a consequence, gravitational effects are obscured on the films much as free intraperitoneal gas — obvious on "upright" films — is likely to be overlooked when radiography of the abdomen is done in the usual prone or supine position. Our interest in the role of gravity grew out of efforts to make more selective the contrast visualization of certain portions of the cardiovascular system, especially the coronary arteries. For a number of years, the relatively high specific gravity of concentrated radiopaque media has been recognized and utilized in achieving rapid and complete delivery to the superior vena cava of the injected agent required by angiocardiography.[4] To this end, the withdrawal of 5 or 10 ml. of blood into the vertically positioned syringe prior to angiocardiographic injection results in a layering of blood on top of the contrast medium. This "floating" blood, delivered last into the patient, propels the contrast medium from peripheral to intrathoracic veins, thereby favoring good visualization.

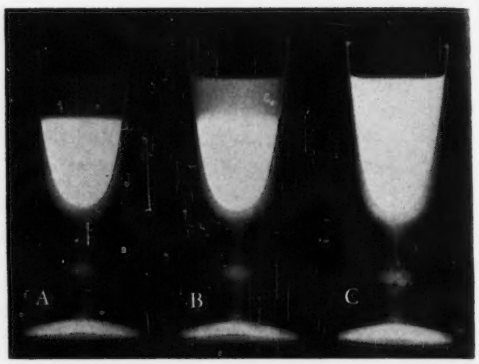

Figure 1

Layering of unmixed blood and contrast agent. Radiograph of 20 ml. of blood layered over 20 ml. of Urokon sodium 70 per cent. A. *Initial sharp interface.* B. *With passage of time and without agitation, loss of separation occurs through spontaneous mixing of two solutions.* C. *Eventually, complete mixing takes place. Disregarding red blood cells, no settling or reformation of layers occurs after mixing.*

Experiments of which figures 1 to 3 are representative were designed to ascertain the extent to which the relatively greater specific gravity of contrast media could be used to enhance selective visualization. As Hol and Skerven[2] pointed out, the layering of contrast agent and blood is present only as long as the two fluids are unmixed. Once mixing has occurred, it is permanent (fig. 1). Incomplete mixing of blood and contrast media can further or defeat the purpose of selective injections, depending upon the velocity and turbulence of blood flow and the distance from the site of injection. A detailed study of the behavior of substances injected into the blood stream has been recorded by Kjellberg.[1]

The injection of 10 ml. of 70 per cent

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This work, done in the Minthorn Memorial Laboratory for Cardiovascular Research through Radiology, was supported by grants from the U. S. Public Health Service (H-3275(C1)), the Oregon Heart Association, and the Mallinckrodt Chemical Works.

*Newton, Sir Isaac: *Philosophial Naturalis Principia Mathematica;* Book III, Proposition 6, Theorem 6, Corollary II; Cambridge, England (1687).

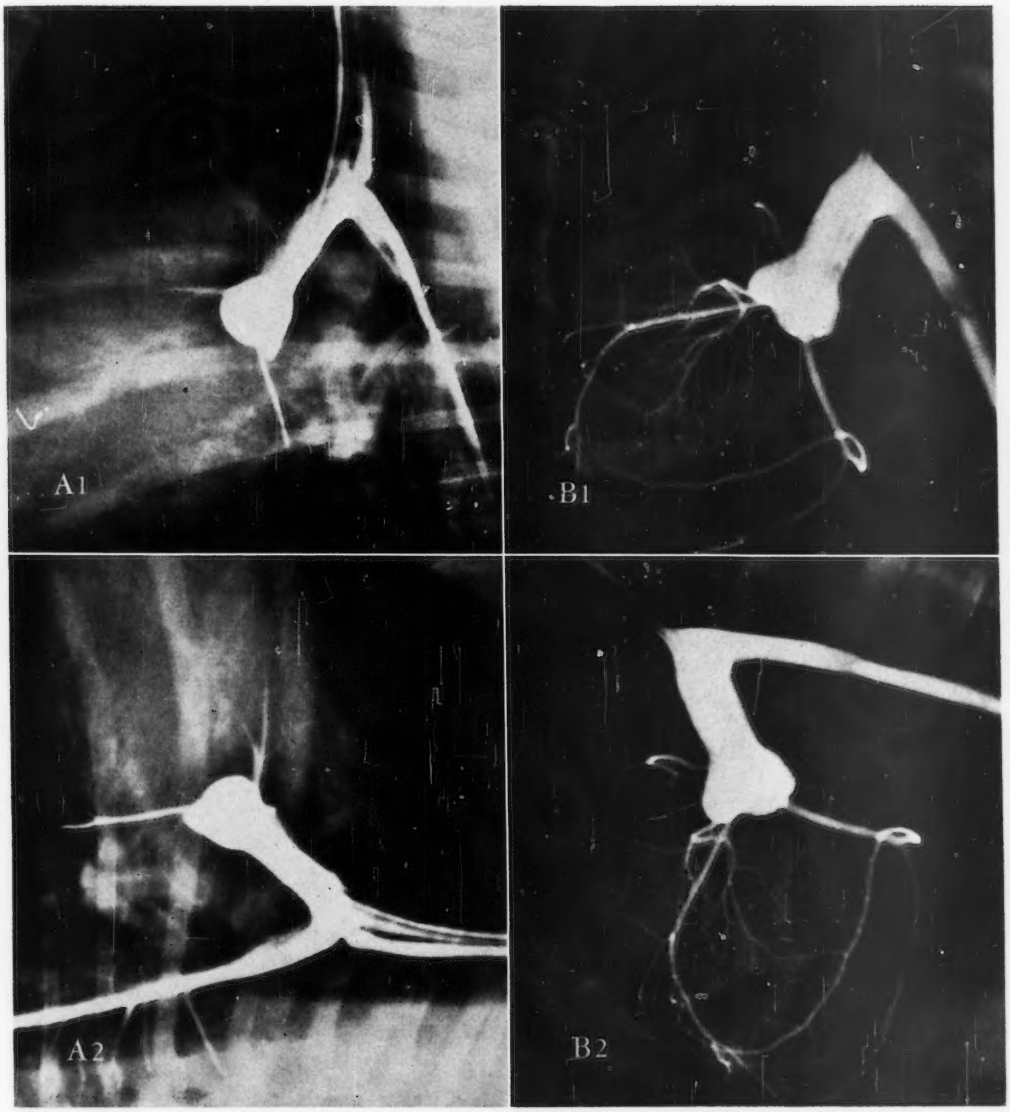

Figure 2

Upright compared to supine position during experimental coronary arteriography during acetylcholine-induced cadiac arrest. A1. *With dog in supine position.* B1. *With dog in upright position. Injections were otherwise identical.* A2 *and* B2 *are succeeding views from the same two injections and have been mounted in the position of visualization. Note the fluid levels in* B1 *and* B2 *and the filling of dependent intercostal arteries in* A2. *Coronary visualization under cardiac arrest is greatly favored by the use of the upright position during the study.*

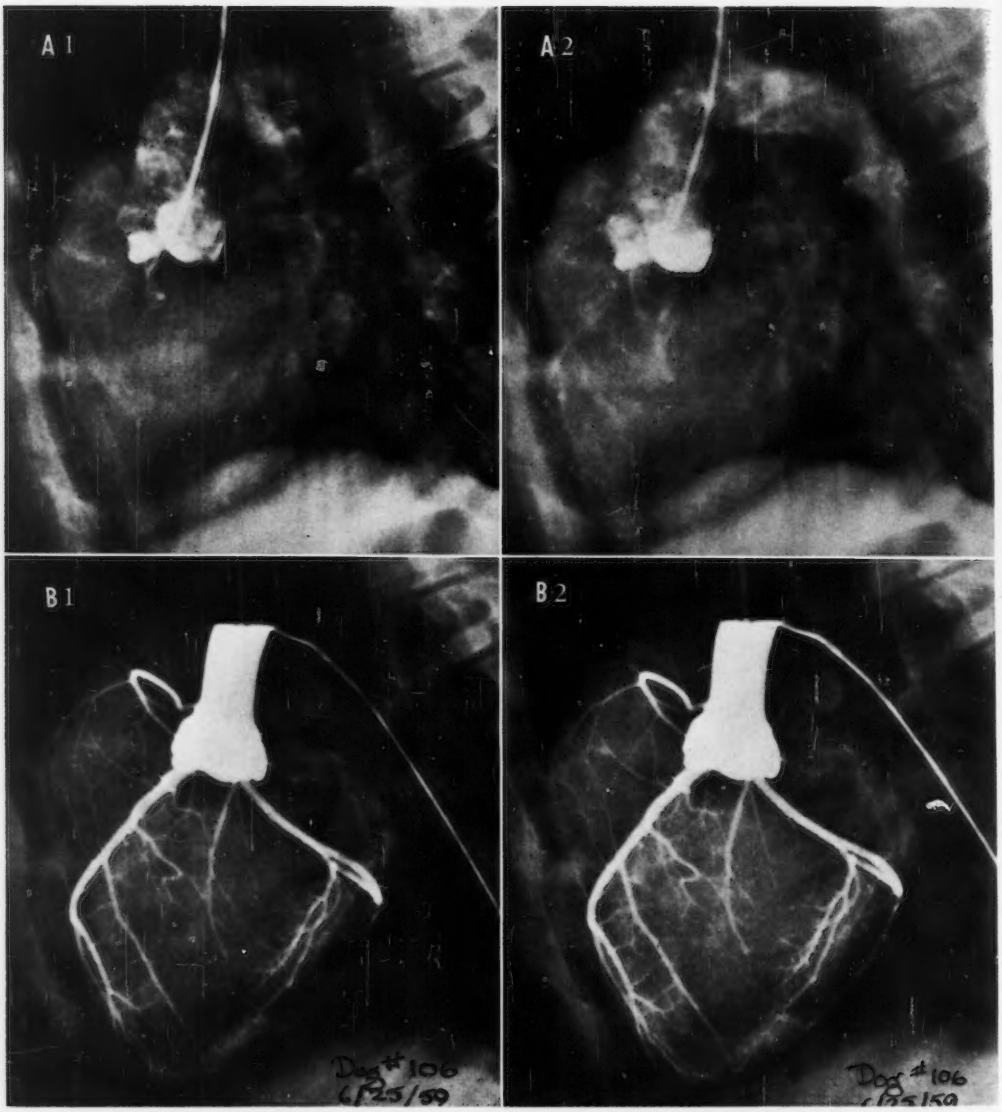

Figure 3

Effects of fluid motion on intravascular mixing of contrast agents during experimental coronary arteriography. A1 *and* A2 *are views during injection made in upright position but without cardiac arrest. Poor coronary visualization due to lack of selectivity among other things.* B1 *and* B2 *are comparable study but injection was done under acetylcholine-induced cardiac arrest. Note high selectivity due to layering of contrast agent in proximal aortic stub. This was prevented in* A1 *and* A2 *by mixing and dispersal due to left ventricular ejection.*

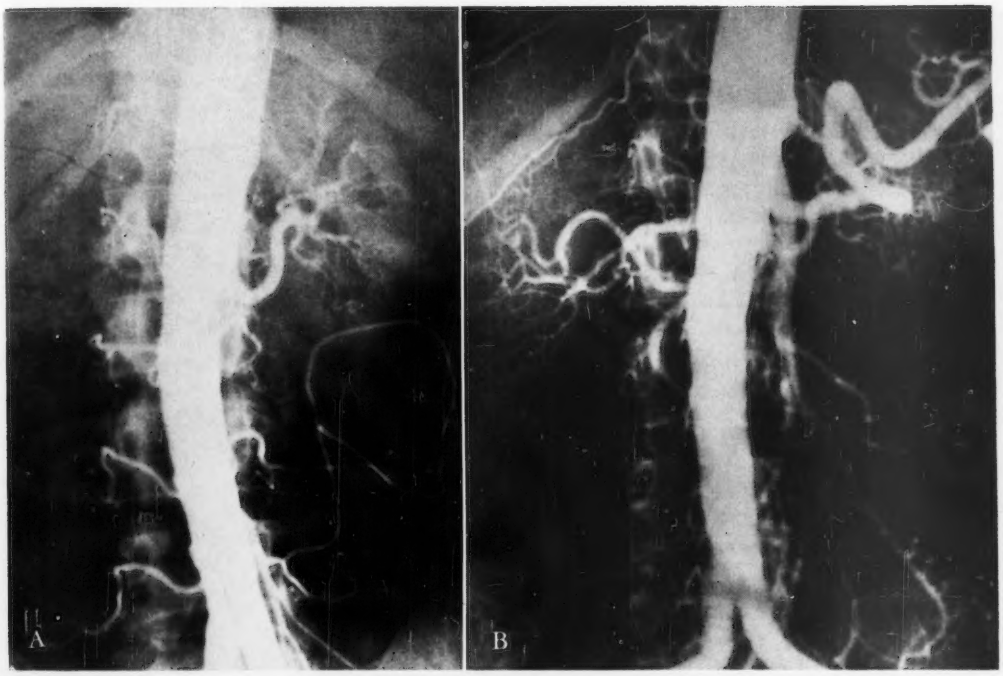

Figure 4

Faulty visualization of one renal and visceral abdominal aortic branches due to effect of gravity during abdominal aortography. Hypertensive 40-year-old woman (UOMS no. 28-01-45). A. *Catheter injection (2 seconds' duration) was done during Valsalva maneuver, with the tip of the catheter at the level of the aortic bifurcation. Blood pressure cuffs were used on both legs. There is good filling of the left renal and dependent lumbar arteries. Nonvisualization of the right renal system and the celiac trunk was an artifact and due to the supine position, the high specific gravity of the contrast agent (Ditriokon, 25 ml.), and other mechanical factors limiting intravascular mixing of the injected agent.* B. *Same patient. Better mixing was favored by a faster injection, higher catheter tip location, and avoidance of the Valsalva maneuver. Note good filling of branches of celiac trunk and visualization of* both *renal arteries.*

sodium acetrizoate (Urokon) with and without cardiac arrest, into the proximal aorta of the dog in the upright and horizontal positions forms a simple, if crude means for experimental appraisal of the effects of specific gravity on the distribution of injected contrast media. A combination of acetylcholine-induced transient cardiac arrest and upright position results in a striking separation of injected media and blood closely resembling the air fluid levels so familiar to radiologists.[5] Even in the presence of a normal cardiac output, the effects of gravity are readily demonstrated (figs. 2 and 3).

It is customary to perform translumbar aortography with the patient in the prone position (since the hub of the needle would make other positions awkward, if not dangerous). Enhanced visualization of the anterior (dependent) branches of the abdominal aorta has been a result of gravity. A supporting corollary has been the common failure of good opacification of the posterior (uppermost) lumbar arteries during translumbar aortography done in prone position. This undesired selectivity is usually avoided when aortography is performed by retrograde catheterization,[6] since the jet resulting from the

forceful injection as well as the side holes in the tubing favors more prompt and more complete mixing of blood and injected substance. Figure 4 illustrates the effects of position during clinical aortography. In this instance, faulty visualization of the right renal artery and major visceral branches of the abdominal aorta resulted from layering caused by (1) circulatory stasis from a Valsalva maneuver, (2) supine position, (3) low position of catheter tip, (4) relatively slow injection. The artifact was recognized and eliminated on a subsequent injection.

Conclusion

Experimental and clinical studies indicate that gravity plays a significant role in the distribution of contrast media injected into the cardiovascular system. Recognized, this factor need not give rise to false interpretation of findings; exploited, it may serve to enhance the selectivity of contrast visualization under appropriate circumstances.

Summario in Interlingua

Studios experimental e clinic indica que le gravitate ha un rolo significative in le distribution de medios de contrasto injicite in le systema cardiovascular. Recognoscite, iste factor non va causar false interpretationes del datos; exploitate, illo de facto pote servir a meliorar le selectivitate del visualisation contrastic sub appropriate circumstantias.

References

1. KJELLBERG, S. R.: Mix and flow relationships of water soluble contrast media in the study of the heart and blood vessels. Acta radiol. **24**: 433, 1943.
2. HOL, R., AND SKERVEN, O.: Spinal cord damage in abdominal aortography. Acta radiol. **42**: 276, 1954.
3. TARAZI, A. K., MARGOLIS, G., AND GRIMSON, K. S.: Spinal cord lesions produced by aortography in dogs. Arch. Surg. **72**: 38, 1956.
4. ROBB, G. P., AND STEINBERG, I.: Visualization of the chambers of the heart, the pulmonary circulation and the great blood vessels in man: A practical method. Am. J. Roentgenol. **41**: 1, 1939.
5. DOTTER, C. T., FRISCHE, L. H., HOSKINSON, W. S. KAWASHIMA, E., AND PHILLIPS, R. W.: Coronary arteriography during induced cardiac arrest and aortic occlusion. Arch Int. Med. **104**: 720, 1959.
6. DOTTER, C. T.: Left ventricular and systemic and arterial catheterization: a simple percutaneous method using a spring guide. Am. J. Roentgenol. **83**: 969, 1960.

Where there is love for humanity, there also is love for the art of medicine.—HIPPOCRATES

Intermittent Atrial Parasystole

By CHARLES FISCH, M.D., AND ROBERT B. CHEVALIER, M.D.

ATRIAL PARASYSTOLE in itself is an extremely rare finding. An intermittent atrial parasystole in which the first beat of each run is a premature atrial systole with fixed coupling to the preceding sinoatrial beat has not been previously described and warrants reporting as an interesting electrocardiographic finding.[1-4] This variant of parasystole may represent an intermediate form between ordinary coupled premature beats and parasystolic rhythm.

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Supported by the Krannert Fund of the Indiana Heart Association, Indiana State Board of Health, and the National Heart Institute (PHS-HTS 5363), U. S. Public Health Service.

The diagnosis of atrial parasystole in our case is based on variable intervals between

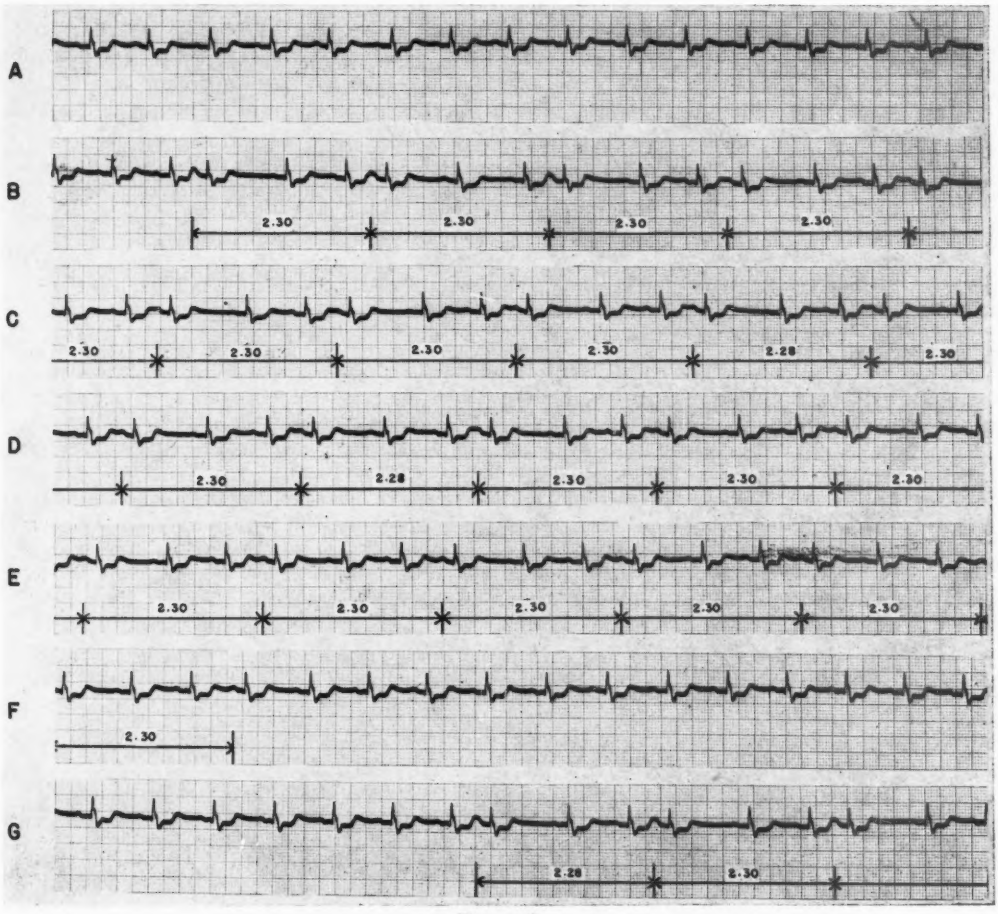

Figure 1

This figure shows an intermittent atrial parasystole. The arrow-heads mark the parasystolic P waves.

the ectopic P waves and the preceding sinus beats in any one run, interference by the premature beat with initiation of the next sinoatrial beat, and the demonstration of a constant time interval between parasystolic P waves. Fusion (combination beats) are not readily apparent in these tracings because the configuration of the sinoatrial and ectopic P waves resembled each other very closely. The parasystolic rhythm is intermittent in character, and all runs of the ectopic rhythm begin with atrial premature systoles at a constant time interval after the preceding sinus beat. Only this initial ectopic beat shows fixed coupling; all the subsequent ectopic beats show variable coupling.

Case Report

The electrocardiogram described below is representative of a number of tracings obtained on different days on a 63-year-old man with severe heart failure, secondary to long-standing hypertensive heart disease. The drugs administered at the time the electrocardiogram was obtained included digitoxin, chlorothiazide, and supplemental potassium.

The strips reproduced in figure 1 form a continuous tracing. Strip A shows a normal sinus rhythm with a P-P interval of 0.72 second. The third P in strip B is premature, follows the preceding sinus beat by 0.50 second, and represents the first atrial wave of a parasystolic rhythm. The P-P interval of the parasystolic focus measures 2.28 to 2.30 seconds. The interval between the ectopic P and preceding sinoatrial beat increases gradually from 0.50 to 0.70 second and as this time approaches the P-P interval of the sinoatrial rhythm (0.72 second), it finds the atrium refractory and the ectopic rhythm is interrupted. In strip G the ectopic P wave reappears again coupled to the preceding sinus P wave, again by an interval of 0.50 second. The time from the last parasystolic P in strip F to the first ectopic beat in strip G is not a multiple of the established parasystolic P-P interval. It measures 15.12 rather than 13.8 or 16.10 seconds, the expected multiple of the established parasystolic interval of 2.30 seconds. The failure of the P wave in strip G to reappear when expected and the constant coupling of the first beat of each parasystolic run indicate that the discharge of the ectopic focus was intermittent or interrupted during this time. The intermittent nature of the parasystole with accurate coupling of the first beat of each cycle was present in over 30 cycles studied.

Summary

A case of atrial parasystole is reported. The parasystolic rhythm was intermittent in character and began each time with an atrial premature beat exhibiting a constant relation to the preceding sinus beat.

Summario in Interlingua

Es reportate un caso de parasystole atrial. Le rhythmo parasystolic esseva de character intermittente e comenciava invariabilemente con un prematur systole atrial, exhibiente un relation constante con le precedente pulso pulso sinusal.

References

1. Katz, L. M., and Pick, A.: Clinical Electrocardiography. Philadelphia, Lea and Febiger, 1956.
2. Scherf, D., and Boyd, L. J.: Three unusual cases of parasystole. Am. Heart J. 39: 650, 1950.
3. —, and Schott, A.: Extrasystoles and Allied Arrhythmias. London, William Heinemann, 1953.
4. —, Yildiz, M., and DeArmas, D.: Atrial parasystole. Am. Heart J. 57: 507, 1959.

SYMPOSIUM ON CORONARY HEART DISEASE

Treatment of Intractable Angina Pectoris

By BRUCE LOGUE, M.D.

ANGINA PECTORIS responds within a few minutes of the administration of sublingual nitroglycerin in the overwhelming majority of instances. Many attacks are prevented by its prophylactic use prior to effort, emotional stress, meals, intercourse, and recumbency. One should be certain that the preparation is effective and has not lost its potency. This can readily be ascertained by the occurrence of the nitrite effect of fullness or throbbing sensation in the head. If this does not occur, a new supply should be obtained. Often after prolonged use of nitroglycerin, effectiveness may be enhanced by increasing the size of the dose from 1/200 gr. to 1/150 or 1/100 gr. At times it may be helpful to use nitroglycerin prophylactically every hour or 2 throughout the day. Nitroglycerin ointment, ½ to 1 inch spread on the skin without massage, may give a sustained nitrite effect for several hours.[1] It is particularly helpful when applied at bedtime to reduce nocturnal attacks. It may be repeated at intervals of 4 hours.

Long-acting vasodilators have limited value. We prefer erythrol tetranitrate (Cardilate), 7.5 to 15 mg. buccally every 2 to 4 hours. Pentaerythritol tetranitrate (Peritrate) 10 to 20 mg. is widely used and is occasionally helpful. The dosage must be individually adjusted to secure full pharmacologic effect with minimum side effects such as headaches.

Weight reduction should be undertaken for the overweight patient. It is a common clinical observation that angina may improve after weight reduction but little may be expected from such a program for frequently recurring pain. A diet low in saturated fats is widely used for weight reduction with the hope that over a long term atherosclerosis may be lessened. There is as yet no evidence that diet or agents to lower the levels of serum cholesterol alter the natural history of atherosclerosis in man.

For those patients who develop angina during or after meals, prophylactic nitroglycerin and frequent small feedings with 5 to 6 meals daily may be indicated. Food should be easily digestible and foods that induce gaseous distention such as cabbage, onions, garlic, dried beans, should be eliminated. Constipation should be avoided by the use of appropriate laxatives. The close relation between distention of the stomach or intestines and development of angina is well known.

Tobacco should be avoided in patients having frequent angina. Occasionally there is a striking decrease in frequency of attacks when smoking is omitted; most individuals, however, notice no change in the pain pattern.

The initial onset of angina pectoris may be related to myocardial infarction. When there is an abrupt change in the pattern of angina pectoris, one should suspect myocardial infarction. This may be the result of further occlusion of a coronary artery or of an increase in the metabolic demands of the myocardium. The latter might be due to prolonged emotional tension, acute infection, blood loss, the onset of cardiac arrhythmia, pulmonary embolism, hypoglycemia, etc. Sharp curtailment of physical activity by a period of several weeks of modified bed rest may be followed, after the development of collateral circulation, by gradual improvement of angina. Since angina, when severe, is commonly

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experienced in the recumbent position, attacks may be lessened by sitting in a chair for most of the day and by having the head of the bed elevated at night.

The classic association between emotional tension and angina demands recognition. The use of sedatives may lessen the frequency of attacks. Heavy sedation over a period of days when emotional factors are dominant may bring improvement. The long-term administration of phenobarbital in the usual doses should be tried. There is rarely any superiority in the host of more expensive tranquilizing agents available on the market. It is probable that the beneficial effect of alcohol is through its effect on the central nervous system rather than any local effect on the heart. Whiskey may relieve mild distress or perhaps lessen attacks but is of little help with frequently recurring and prolonged attacks. The patient-physician relation is important, and strong reassurance and expert handling by the knowledgeable physician may produce benefit. Some patients with severe angina pectoris improve spontaneously, and every patient should be informed of this fact. False optimism may back-fire but the knowledge that his condition is not necessarily static and irrevocable may help sustain the weary patient. Reactive depression should be sought for and treated. In our opinion, the early successes with the amine oxidase inhibitor drugs were probably due to their effect on the mental depression that so often darkens the picture in severe angina pectoris. These drugs do not alter the electrocardiogram or the underlying coronary disease, and their use is associated with side effects that include postural hypotension. They should not be used routinely in the treatment of angina but reserved for trial in selected patients with refractory angina.[2]

Arrhythmias including frequent premature beats may aggravate angina. Control of arrhythmias occasionally is beneficial. Frequent premature beats may at times be associated with myocardial insufficiency otherwise unrecognized, and digitalization may dissipate the arrhythmia and lessen the attacks. In the digitalized patient, the occurrence of coupling, paroxysmal atrial tachycardia with atrioventricular block, interference dissociation, ventricular tachycardia, atrial flutter or fibrillation, demands temporary omission of the drug and determination of the need for potassium replacement. Cellular depletion may occur despite normal serum values for potassium. Persistent arrhythmias in the euthyroid patient may respond to the induction of hypothyroidism by I^{131}. Kurland et al.[3] have reported instances of recurrent arrhythmias in euthyroid patients associated with rapid turnover of thyroxine in the red cells that respond to large doses of inorganic iodine. Quinidine on occasion may lessen angina through prevention of arrhythmia.

Where nocturnal angina occurs, a trial period of digitalization is advisable even though usual symptoms and signs of left ventricular failure may be lacking. Elevation of the pulmonary artery and pulmonary capillary pressures may occur during angina in patients with hearts of normal size.[4] Often times digitalization is followed by lessening of the attacks. Chlorothiazide, 500 mg. daily, combined with accessory potassium salts may bring benefit through lessening interstitial pulmonary congestion and perhaps its effect in lowering the blood volume. It is not widely appreciated that mild left ventricular failure may occur without diastolic gallop rhythm, rales, or paroxysmal nocturnal dyspnea and in the presence of a heart of clinically normal size.

Rauwolfia derivatives are generally ineffective but in the occasional patient with anxiety and sinus tachycardia may be beneficial. The frequency of side effects, particularly the development of mental depression (up to 20 per cent of cases), limits their use. Benefit may result from a combination of their psychic effect combined with slowing of the pulse rate. Their use should be undertaken only on a trial basis, with their common side effects well in mind and with the caution that mental depression may appear only after many months of therapy.

When significant hypertension is present,

anginal attacks may lessen with lowering of the blood pressure. Caution should be exercised, since bouts of prolonged pain may be induced if the blood pressure drops too low. In general, one depends on chlorothiazide derivatives with or without a Rauwolfia preparation and reluctantly adds one of the ganglion-blocking agents, since they are dangerous. Apresoline should be used cautiously, and only in doses of less than 100 mg. per day because of the frequency of tachycardia and pain with larger doses. The benefits from lowered blood pressure are more marked in the management of congestive heart failure than in the treatment of angina pectoris. The place of monamine oxidase inhibitors and the newer sympatholytic drugs in the management of hypertension is still to be determined.

Anginal attacks of 5 to 15 minutes in duration may be managed with some degree of success; however, the common occurrence of prolonged bouts of pain requiring opiates is the greatest problem in the field of coronary disease. Such attacks occur independently of usual precipitating causes and may not be accompanied by evidence of muscle necrosis such as electrocardiographic changes, fever, elevated sedimentation rate, and elevations of serum enzymes. Subendocardial infarction of a patchy nature may occur in electrically silent areas. Such attacks may be repeated over a period of many months and may eventuate in drug addiction. The precipitating factor remains unknown at this time, but the possible effects of release of increased amounts of catechol amines are under study. Only rarely does collateral circulation develop sufficiently to bring spontaneous improvement. One often wishes for transmural infarction, with the hope that alleviation will follow destruction of the pain-producing focus. Prinzmetal et al.[5] have reported that Arlidin is of value, presumably by reducing spasm of the coronary arteries; but we have been unable to confirm its value.

When angina is frequent and disabling, and when repeated bouts of prolonged pain have occurred and the condition has not improved over a period of 3 months, the production of hypothyroidism by the use of radioactive iodine offers the best hope of benefit. It requires 2 to 3 months before an optimal effect is obtained and occasionally even longer. I^{131} may be given in a single dose or in repeated doses. Thyroiditis may at times be produced, but responds to a brief period of steroid therapy. The side effects of myxedema may be troublesome. Paresthesias and pains in the extremities, abdominal swelling, puffiness of the face, drowsiness, anemia, and weight gain are the most distressing symptoms. At the onset of symptoms a small dose of thyroid such as 1/10 to ¼ gr. is instituted. Increments are made at intervals of 7 to 10 days, depending upon tolerance until a level is reached at which pain and side effects are minimal. About two-thirds of patients receive benefit of varying degree, and one-third are unaffected. Blumgart and associates[6] reported that 43 per cent of 84 patients obtained excellent results, 24 per cent had worthwhile results, and 33 per cent had no benefit. In a previous combined study from a number of clinics about 75 per cent of 1,070 patients with angina showed improvement.[7]

Patients with thyrotoxicosis may have dramatic improvement of angina when normal metabolism is restored. Study of serum protein-bound iodine and I^{131} uptake is valuable in the detection of masked thyrotoxicosis. Furthermore, the use of scanning technics in the presence of an adenoma may at the times reveal toxicity even when other studies are normal. The administration of I^{131} in appropriate doses or thiouracil derivatives may bring lasting benefit.

Angina pectoris secondary to congenital or acquired aortic stenosis may be alleviated following aortic commissurotomy; the trend at this time is surgical correction using open-heart technics with or without coronary artery perfusion. The surgery of aortic stenosis when it has become symptomatic still leaves much to be desired. When angina is secondary to aortic insufficiency, the patient is under 50 years of age, and congestive heart failure can be controlled, surgery with the insertion of a Hufnagel valve may be bene-

ficial. In Hufnagel's hands the risk approaches 15 per cent.[8]

Syphilitic aortitis may produce angina pectoris either by swelling and narrowing of the coronary ostia or by development of free aortic insufficiency. Antisyphilitic therapy with penicillin does not alter the disease at this stage but should be given in the customary schedule of 600,000 units of procaine penicillin daily for 10 days.

Anticoagulants are widely employed in the long-term treatment of coronary disease, but they do not alter the course of angina pectoris. Many times they are used in the hope that infarction might be prevented or forestalled in the face of increasing frequency of angina. In one series 6 per cent of 96 treated patients died, whereas 19 per cent of 32 who stopped anticoagulants died, and another 4 of 10 controls with impending infarction died.[9] The data are still inconclusive. Anticoagulants should be used in any instance in which there is suspicion of pulmonary embolism. Refractory angina often improves when thromboembolism is controlled. Some have recommended intermittent heparin in the management of angina but a beneficial effect has not been corroborated by other studies.

As with all therapy, medical or surgical, placebo effects make evaluation of any drug or surgical procedure difficult. Ligation of the internal mammary artery is an example with claims of benefit in about 60 per cent of patients; but double-blind studies did not bear out the previous uncontrolled experience.[10] The revascularization procedure of Beck and Leighninger,[11] consisting of abrasion of the epicardium by a burr, instillation of powdered silicate, and subtotal ligation of the coronary sinus, has few adherents. The Vineberg procedure[12] of implantation of the internal mammary artery in the myocardium is of debatable value.

Harken et al.[13] claimed that improvement of pain follows the application of phenol on the epicardium, presumably through destruction of pain fibers, but we have observed no substantial benefit in a small group of cases. Thromboendarterectomy of the coronary arteries is still in the experimental phase; of 11 severely ill patients died of the procedure.[14] Grafting of segments of a vessel has been impractical because of invariable thrombosis, and the problems of direct relief of coronary occlusion are numerous.[15] Sympathectomy and rhizotomy for relief of pain may require bilateral operations, and rhizotomy entails laminectomy. The risk of anesthesia in patients with refractory angina is great. Painful causalgia is common following sympathetic nerve surgery and may be more distressing than pain of coronary disease over the period of months of its duration.

Diabetes is a common accompaniment of coronary disease. When mild it may be well controlled by diet or oral or hypoglycemic agents such as Orinase, 0.5 to 1.0 Gm. 3 to 4 times daily. There is no evidence that rigid control of diabetes alters the course of coronary disease. Attempts to control glycosuria and hyperglycemia strictly with medication are fraught with dangers of hypoglycemia. Such attacks may induce angina or myocardial infarction. The use of NPH or globin insulin in appropriate amounts for more severe diabetes is indicated. When diabetic acidosis occurs, epigastric pain simulating coronary pain may occur and the problems of differentiation are made more difficult by the changes in the ST-T interval due to potassium shifts. These include prolongation of Q-U interval, S-T depression, and T-wave inversion. Since myocardial infarction may occur without the complaint of pain in the stuporous patient and since infarction may induce diabetic acidosis, it is well routinely to check the electrocardiogram when there has been an otherwise unexplained abrupt change in the diabetic state. For the patient who has been receiving protamine zinc insulin and develops refractory angina pectoris or myocardial infarction, it is desirable to change to regular or Lente insulin until the condition is stabilized.

Treatment of anemia may change refractory angina to one that is readily amenable. The increase in oxygen-carrying capacity of hemoglobin may be obtained by appropriate

therapy such as iron or vitamin B_{12}. Occasionally, when blood loss has occurred, rapid replacement may be needed with transfusion of red cells to avoid pulmonary edema.

Angina of brief duration related to usual precipitating causes may become refractory with the onset of infection and the consequent increase in metabolic demands. Prompt recognition and appropriate treatment of pulmonary infection, urinary tract infection, and gallbladder disease may be beneficial. The relief of overlooked urinary tract obstruction such as that due to prostatic disease may lessen anginal attacks. The common occurrence of associated gallbladder disease poses a problem. Cholecystectomy with prevention of recurrent infections may lessen bouts of pain; it is to be emphasized, however, that such surgery has no direct effect on the coronary circulation. Furthermore, in the presence of angina decubitus the risk of general anesthesia and any type of major surgery approaches 50 per cent. Elective surgery in the patient with a history of angina pectoris on effort, on the other hand, carries a risk on the order of 5 per cent.

Summario in Interlingua

Es revistate le currentemente disponibile medios in le tractamento de angina de pectore. Le revista include le medios medical e etiam chirurgic.

References

1. DAVIS, J. A., AND WEISEL, B.: Treatment of angina pectoris with nitroglycerin ointment. Am. J. M. Sc. 230: 259, 1955.
2. JOLLY, E. R.: Editorial. Circulation 20: 1, 1959.
3. KURLAND, G. S., GOLODETZ, A., HAMOLSKY, M. W., and FREEDBERG, A. S.: Thyroid function in supraventricular tachycardia: Turnover of intravenously infused I^{131} labelled thyroxine and the red blood cell uptake of I^{131} labelled 1-triiodo thyronine. J. Clin. Endocrinol. & Metab. 19: 92, 1959.
4. MÜLLER, O., AND RORVIK, K.: Hemodynamic consequences of coronary heart disease. Brit. Heart J. 20: 302, 1958.
5. PRINZMETAL, M., KENNAMER, R., MERLISS, R., WADA, T., AND BOR, N.: Angina pectoris I, A variant form of angina pectoris. Preliminary Report. Am. J. Med. 27: 375, 1959.
6. BLUMGART, H., FREEDBERG, A. S., AND KURLAND, G. S.: Radioactive iodine treatment for angina pectoris and congestive heart failure. Clinical Conference. Circulation 16: 110, 1957.
7. —, —, AND —: Treatment of incapacitated euthyroid cardiac patients with radioactive iodine. J.A.M.A. 157: 1, 1953.
8. HUFNAGEL, C. A.: Current status of operation for aortic insufficiency. Progress in Cardiovascular Disease, Vol. 1, New York, Grune & Stratton, Inc., 1958, p. 41.
9. NICHOL, E. S., KEYES, J. N., BORG, J. T., COOGAN, T. J., BOEHNER, J. J., MULLINS, W. L., SCOTT, T., PAGE, R., GRIFFITH, G. C., AND MASSIE, E.: Long term anticoagulant therapy in coronary atherosclerosis. Am. Heart J. 55: 142, 1950.
10. COBB, L. A., THOMAS, G. I., MERENDINO, K. A., AND BRUCE, R. A.: An evaluation of internal mammary artery ligation by a double blind technique. New England J. Med. 260: 1115, 1959.
11. BECK, C. S., AND LEIGHNINGER, D. S.: Operations for coronary artery disease. J.A.M.A. 156: 1226, 1954.
12. VINEBERG, A., MUNRO, D. C., COHEN, H., AND BUTLER, W.: Four years' clinical experience with internal mammary-artery implantation in the treatment of human coronary artery insufficiency including experimental studies. J. Thoracic Surg. 29: 1, 1955.
13. HARKEN, D., BLACK, H., DICKSON, J. F., III, AND WILSON, H. E., III: De-epicardialization: A simple, effective surgical treatment for angina pectoris. Circulation 12: 955, 1955.
14. KATTUS, A., LONGMIRE, W. P., CANNON, J. A., WINFIELD, M. E., AND DAVIS, J. H.: Diagnostic and functional evaluation of candidates for coronary endarterectomy. Arch. Int. Med. 104: 862, 1959.
15. BLUMGART, H. L., ZOLL, P. M., AND KURLAND, G. S.: Discussion of direct relief of coronary occlusion. Arch. Int. Med. 104: 862, 1959.

Amine Oxidase Inhibitors

Their Current Place in the Therapy of Cardiovascular Diseases

By GEORGE C. GRIFFITH, M.D.

WE HAVE HAD a keen interest in the monoamine oxidase inhibitors (MAO-inhibitors) from the time that Cesarman[1] first reported their benefits in the prophylaxis of angina pectoris. Together with two of my associates, Dr. Robert W. Oblath and Dr. Willard J. Zinn, I have used four of the available MAO-inhibitors—iproniazid, isocarboxazid, beta-phenylisopropylhydrazine, and pivalylbenzhydrazine—in the treatment of patients with myocardial ischemia. In general we find that our patients feel better under medication with iproniazid and its analogues than they had felt prior to the administration of these products. They are more alert, more cheerful, and they can do more than was possible formerly. As other investigators have noted, under treatment with MAO-inhibitors patients previously disabled by angina are able to walk distances heretofore out of the question for them and—as long as they are receiving adequate dosages of these drugs—they can go about their daily activities within the limits dictated by the state of the myocardium and prescribed for them by their physicians without experiencing anginal pain or even pressure. Once the drug is stopped or reduced below the effective level for the individual patient, his capacity for effort again becomes increasingly limited, and he is forced to return to his pretreatment inactivity.

Patient-physician rapport is tremendously improved under the influence of the MAO-inhibitors. The patient assumes a healthier attitude toward his disease and a more hopeful outlook toward the future outcome. Whereas he remains aware of petty annoyances, he now reacts toward these with emotional detachment. Usually, tension and depression give way to a state of relative tranquility.

First employed for its tuberculostatic and tuberculocidal properties alone, iproniazid administration was found to confer many other important benefits, of which at least two—relief of pain and the healing of mesodermal tissue—bear directly on the problem of pain prophylaxis in cardiovascular disease. Under iproniazid therapy the influence toward healing of mesodermal tissue has proved out of proportion to any influence of the chemical on the tubercle organism alone. Relief from pain has been such that in one patient with an extensive destructive neoplasm of the right pelvis, iproniazid administration has permitted increased hip movement and the discontinuance of 200 mg. of Demerol every 3 hours.[2]

Because of its potent appetite-stimulating effects, iproniazid has been employed with profit in the treatment of poor appetite due to hepatitis, cirrhosis, anorexia nervosa, poor nutritional state due to duodenal ulcer, ulcerative colitis, geriatric wasting, and chronic or psychogenic nausea without definite evidence of organic disease.[3]

As contentment and even feelings of elation often replace initial depression in tubercular patients maintained on iproniazid, this preparation and several of its analogues have been widely used in the treatment of hypoactive and depressed psychiatric patients. As anticipated, the antidepressive types of MAO-inhibitor are effective in most cases of depression, whatever the origin, and offer many advantages over electroconvulsive therapy, heretofore the only effective treatment of the depressed psychiatric patient.[4] In addition to

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its beneficial effects on mood and activity, iproniazid administration has been found to increase physician-patient rapport: the patient both seeks and is additionally receptive to support and reassurance.

All these elements—pain relief, healing of mesodermal tissues, appetite stimulation, closer physician-patient rapport, and elevation of mood—are most important in the therapy of the patient with angina pectoris, who not only is limited in his capacity for effort but usually is very fearful of the outcome of his illness.

Biochemical and Physiologic Results of MAO-Inhibition

The effect of MAO-inhibitors on serotonin metabolism has received particularly close attention, inasmuch as iproniazid administration increases brain serotonin levels to 2 or 3 times normal.[5] Following a single dose of iproniazid, the highest brain serotonin level is attained within 3 to 5 hours and tapers off within a few hours;[6] repeated doses administered over several days do not raise brain serotonin levels above the concentration produced by a single dose.[7] Iproniazid has been shown to have little effect on the peripheral metabolism of serotonin, with no increase of serotonin determinable in blood, stomach, or intestines, despite the marked increase in brain serotonin.[6]

Apparently, iproniazid does not exert a significant effect on the concentrations of epinephrine or norepinephrine;[8] the primary effect of iproniazid seems to be not on the level of the amines themselves but on their *metabolites*. As measured by the metabolism of methyl-labeled epinephrine, the biochemical effects of iproniazid in man persist for 2 or 3 weeks after cessation of iproniazid therapy.[9] Some investigators believe that iproniazid may in some way convert the tension created by epinephrine into the euphoria often noted in the patient maintained on iproniazid—perhaps by the diversion of epinephrine or methoxyepinephrine to adrenochrome or its derivatives.[10] Patients who suffer from anxiety or tension destroy adrenochrome more rapidly than normal subjects do;[11] and following the administration of adrenochrome or adrenolutin, anxiety steadily decreases.[10]

The central stimulant effects of iproniazid appear to be due at least in part to the action of dopamine.[12] Other amines that are affected by iproniazid administration include tyramine[13] and tryptamine.[14] In man, assay of urinary tryptamine affords a simple measure of MAO-inhibition that appears to be a reflection of MAO-inhibition throughout the body.[14] Neurophysiologic studies suggest that central nervous stimulation of iproniazid probably is achieved through an effect on the hypothalamus.[15–17]

Possible Bases for Antianginal Effectiveness of MAO-Inhibitors

Since the admittedly fortuitous discovery by Cesarman[1] that iproniazid relieves the pain of angina pectoris, a growing number of investigations have been designed to determine the possible bases for the alleviation of chest pain by these preparations. The first possible basis that comes to mind is, of course, a *psychic element*. Inasmuch as MAO-inhibitors purportedly increase physician-patient rapport and would therefore make the patient especially susceptible to the placebo effect so important in the evaluation of antianginal medications, careful double-blind investigations of the efficacy of MAO-inhibitors are most important, such as the study conducted by Shoshkes and his co-workers[18] at Newark Beth Israel Hospital. In this 6-month study, 64 per cent of patients in this series received good or excellent relief from their angina within the first month on iproniazid (23 per cent, good; 41 per cent, excellent), and 72 per cent received good or excellent relief within the second month (10 per cent, good; 62 per cent, excellent). Substitution of the placebo caused a marked and sudden falling off of improvement, with only 5 per cent of the patients claiming excellent response and 25 per cent a good response. This would indicate that although a psychic element undoubtedly is involved in the effectiveness of iproniazid—as with any medication—this psychic element is not the most important or even a

Table 1

Ten Hydrazides That Have Received Considerable Use as MAO-Inhibitors

Iproniazid (1-isonicotinyl-2-isopropylhydrazine)
Isocarboxazid (1-benzyl-2-[5-methyl-3-isoxazolylcarbonyl]hydrazine)
JB-516 (beta-phenylisopropylhydrazine)
Phenelzine (beta-phenylethylhydrazine)
Nialamide (1-isonicotinyl-2-[beta(benzylcarbamyl) ethyl] hydrazine)
Pivalylbenzhydrazine (1-benzyl-2-[trimethylacetyl] hydrazine)*
Ro 4-1027 (1-[p-chlorobenzoyl] -2-isopropylhydrazine)
Ro 4-1038 (DL-serine isopropylhydrazine)
Ro 4-1385 (L-glutamic acid a-isopropylhydrazine)*
Ro 5-0700 (1-benzyl-2-picolinylhydrazine)*

*The hydrazides generally cause increased drive and activity. Notable exceptions are glutamic acid hydrazine, pivalybenzhydrazine, and benzylpicolinylhydrazine, which tend to depress drive and activity: when 1 of the 3 preparations is administered to patients suffering from psychomotor agitation or hyperactivity, considerable clinical improvement results, followed by an elevation in mood. However, if administered to patients already depressed and inhibited, glutamic acid hydrazine, pivalylbenzhydrazine or benzyl-picolinylhydrazine intensifies the syndrome of dullness, increased fatigue, and lack of initiative.

major factor in the antianginal effect of the medication.

Hard to distinguish from the psychic element of angina and antianginal prophylaxis is the possibility of a specific *rise in the pain threshold*. For a time the belief was prevalent that the entire antianginal effect of these preparations is due to their antidepressant effect; however, the development of a number of MAO-inhibitors that further depress rather than increase drive and activity indicates that the noteworthy antianginal effect of the MAO-inhibitors is quite separate from their antidepressant effect. In table 1, 3 preparations that decrease rather than increase drive and activity are identified by asterisks.

Iproniazid, beta-phenylisopropylhydrazine, and related compounds have been shown to possess *analgesic activity* up to the efficacy of codeine.[19] This analgesic activity is particularly noteworthy when mesenchymal tissues are involved, although MAO-inhibitors also have been used successfully to replace narcotics in addicted individuals and have been demonstrated to potentiate the peripheral analgesic activity of 5-hydroxytryptophan and of DOPA.[20]

Central nervous system stimulation probably is important in the analgesic effects of the MAO-inhibitors. The antidepressant effects of these preparations are more likely to occur if psychomotor retardation has been present prior to treatment. Often the amount of initial psychomotor retardation is not apparent until after the improvement caused by the MAO-inhibitors. The high levels of MAO-inhibitors in spinal fluid and brain as compared with blood serum and other body tissues suggest that the central nervous system is intimately involved in MAO-inhibition.

Because of the many points of similarity between the clinical effects of *ganglionic blockade* and iproniazid administration, a relationship has been postulated between ganglionic blockade and the antianginal attributes of MAO-inhibitors. Certain of the side effects of MAO-inhibition are treated as if ganglionic blockade were in fact involved. Nevertheless, MAO-inhibitors have been found to block ganglia only if perfused directly through isolated ganglia.[21]

The antianginal effect of these preparations may be due in part to their *oxygen-sparing effect*. Pretreatment with isocarboxazid protects against the severe, infarct-like myocardial necroses which follow intraperitoneal injection of isopropylarterenol into rats on 2 successive days. Inasmuch as such necroses are due to increased oxygen consumption and drop in blood pressure, lessened severity of such myocardial necrosis following isocarboxazid may be interpreted as evidence of an oxygen-sparing effect, probably due to interference in some oxidative process.[22]

A seventh avenue of investigation is possible *coronary dilatation*. The MAO-inhibitors have been shown to cause coronary dilatation in the isolated heart[23, 24] and in the intact animal,[25] and serotonin—itself a dilator substance—is present in the blood after MAO-inhibitor administration.[26, 27] Several circumstances, however, make it unlikely that either inhibition of MAO per se or the rise in blood

serotonin levels following MAO-inhibitors is important in the relief of angina pectoris: coronary dilatation is of very short duration, unlikely to provide chronic relief of anginal pain, and, as patients who need and respond to MAO-inhibitors usually suffer from advanced atherosclerosis of the coronary arteries, some question exists whether this type of diseased coronary artery would be able to dilate significantly in response to amine potentiation.

Cardiovascular Effects of the MAO-Inhibitors

In assessing the cardiovascular effects of the MAO-inhibitors, one must keep 3 factors in mind: the natural history of the disease, the recognized tendency for these patients to look for and to exaggerate the magnitude and importance of untoward reactions, and the placebo effect of the medications. At times it is difficult to ascertain whether events occurring during the course of medication have been caused by the medication or are the natural result of the underlying cardiovascular pathology.

Effects on Blood Pressure

Although instances of orthostatic hypotension stemming from the administration of iproniazid have been noted during the treatment of patients with tuberculosis and psychiatric depression, attention usually has been directed at the dangers of physical injury from falls attributable to hypotension, especially in elderly persons. Only recently has attention been focused on possible cardiovascular effects of the MAO-inhibitors. Investigators have been sharply divided into 2 camps: those who feel that the drugs should be withheld from persons with known cardiovascular impairment inasmuch as they tend to cause hypotension and thus may precipitate cerebrovascular accidents,[28, 29] and physicians who believe as strongly that such events are the natural occurrence in cerebrovascular disease and that the MAO-inhibitors do not increase the likelihood of cerebrovascular accidents.[30] In general, we agree with the second group and, when indicated, we do not deny MAO-inhibitors to patients despite the presence of cerebrovascular disease.

The hypotensive effects of the MAO-inhibitors have led to their trial as antihypertensive agents, both alone and in combination with chlorothiazide, which has an antihypertensive tendency itself. Thus, Harnes[31] noted a definite orthostatic hypotensive effect in 15 of 17 patients (88 per cent); in 5 of these patients, blood pressure was also reduced when in the supine position. Nussbaum[32] reported the reduction of blood pressure in 17 of 22 hypertensive patients (77 per cent): 1 patient had been taken off mecamylamine, 15 mg. t.i.d.; when iproniazid, 50 mg. t.i.d., was substituted for the ganglion-blocking agent, his base blood pressure dropped from 170/140 without medication and 150/100 while he was receiving mecamylamine, to 110/70 while receiving iproniazid. Orvis and Tamagna[33] and Maxwell[34] have found iproniazid plus chlorothiazide or beta-phenylisopropylhydrazine plus chlorothiazide to constitute an effective antihypertensive regimen.

Patients with hypertension of severe degree require much decreased dosage of other antihypertensive medication to maintain safe blood pressure levels while taking MAO-inhibitors. Goldman[35] discusses 1 patient who had required 800 mg. of hydralazine daily to maintain a level of 150 mm. systolic: this level was maintained with 150 mg. of iproniazid and only 100 mg. of hydralazine per day.

The action of beta-phenylisopropylhydrazine on blood pressure is similar to that of ganglion-blocking agents, according to Sjoerdsma et al.:[38] the MAO-inhibitor is superior in that it permits continual control with a once-a-day dose and avoids the side effects of impotency, mydriasis, and severe constipation. Cesarman,[30] who considers iproniazid to be a ganglioplegic agent, reports that iproniazid is helpful in reducing blood pressure in patients who have not responded to or who have been unable to tolerate other blocking agents.

Cautioning that alterations in coronary circulation and consequent thrombosis may be induced by falls in blood pressure during shock, Master and Donoso[37] suggest that MAO-inhibitors may be contraindicated in patients with regularly low blood pressure (less

than 100 mm. Hg, systolic), as often is the case in patients who have recently recovered from a coronary occlusion.

In an occasional patient, hypertension rather than hypotension results from the administration of MAO-inhibitors. One patient in our series, who had been maintained satisfactorily on iproniazid, developed hypertension when isocarboxazid was substituted for the iproniazid. Return of the patient to iproniazid resulted in a drop in blood pressure level toward but not to former levels.

Effect in the Anginal Syndrome due to Coronary Artery Disease

The MAO-inhibitors diminish both the intensity and frequency of anginal pain and increase the capacity for exertion. As Cesarman[30] has noted, the greater the severity of pain, the more pronounced is the therapeutic response: After 90 days of treatment, 98 per cent of his patients who had had pain in clinostatism were improved, as were 95 per cent who had had pain on slight exertion, 96 per cent who had had pain on moderate exertion, and 86 per cent who had suffered pain only with great exertion. Rivier[38] has reported success in 75 per cent of 75 cases observed for periods of 2 to 11 months; Cossio[39] has had good results in roughly 2 of 3 patients in a series of 300 whom he has maintained on the drug. These findings are typical of results in other series reported in the literature. We have found good or excellent results in about 70 per cent of our own patients.

There is some question whether the MAO-inhibitors merely exert a symptomatic effect or whether they possibly cause an increase in the efficiency of the heart muscle itself. Cesarman[30] and Rivier[38] believed that iproniazid must exert a direct action at the level of the myocardium. Master,[40] Schweizer,[41] and Wolffe and Shubin[42] found no evidence that the underlying pathology is improved. If the MAO-inhibitors should result in significant improvement in the electrocardiogram, this might be interpreted as evidence that these preparations do improve myocardial action. Cesarman[30] found favorable electrocardiographic modifications in some instances, which he suggests may be caused by a decrease in vasoconstrictor tone of the coronary vessels with increased coronary flow and cardiac output. Schweizer and von Planta,[28] Cossio[39] and Master[40] failed to note any improvement. Nevertheless, LaDue (personal communication) is reported to have noted improvement in the electrocardiograms of patients studied with his "walking electrocardiogram."

Effects on the Peripheral Vasculature

Reports of the effects of MAO-inhibitor administration on intermittent claudication are mixed, with several investigators[42, 43] reporting intermittent claudication as occurring for the first time under MAO-inhibitor therapy, and others[44] reporting dramatic benefit in this condition. Casselas[46] described a patient who had been unable to walk 50 meters prior to iproniazid therapy, but who is able to walk a distance of 1,250 meters (¾ mile) without pain or discomfort while on MAO-inhibitor therapy. Cossio[45] found that half of the patients in his series could cover longer distances, yet in the end pain always forced them to stop and rest. Presumably, cases of intermittent claudication noted for the first time while the patient is under MAO-inhibitor therapy are not a direct effect of the drug: alleviation of anginal symptoms in these previously restricted persons enables them to walk, thereby making evident their latent peripheral circulatory insufficiency.[42]

Color, temperature, and arterial oscillations remain unchanged in the distal segment of the lower limbs.[45] Nevertheless, one instance of impending gangrene observed by Cossio[45] showed an improved blood supply, which ruled out a probable amputation. Cossio found iproniazid very effective against the excruciating pain of impending gangrene. Sherbel and Harrison[46] found an ointment containing 3 to 5 per cent of iproniazid ineffective when applied to ischemic ulcers associated with arteriosclerosis obliterans.

Infarction during MAO-Inhibitor Therapy

As serotonin is highly concentrated in the platelets, serotonin is believed to reduce the duration of local bleeding. Holtz[47] has sug-

gested that, as potentiators of serotonin, the MAO-inhibitors may influence the formation of thrombi and infarction. No evidence has been produced that this is indeed the case. There is evidence, however, that iproniazid administration may increase chances of survival if coronary occlusion occurs. As Regelson et al.[48] have shown, iproniazid administered for 4 days prior to the onset of acute coronary occlusion prevents death in dogs by protecting them from the rapid onset of ventricular fibrillation.

Preparations Available for Use

As more and more MAO-inhibitors become available for clinical trial and, subsequently, for use in the treatment of cardiovascular problems and in other conditions, physicians will be able not only to tailor dosage to the individual needs of the patient but also to choose the specific MAO-inhibitor (or type of inhibitor) that will cause optimal improvement in the patient's condition. Five preparations have undergone extensive clinical trials in this country: iproniazid, isocarboxazid, beta-phenylisopropylhydrazine, nialamide, and phenelzine.

Iproniazid

The first and most widely used of the MAO-inhibitors, iproniazid, is accepted as the standard of MAO-inhibitor action, and other preparations are referred to as having "so many times the potency of" iproniazid. When used in the massive dosages needed in the therapy of tuberculosis or even in the somewhat lesser dosages that first were used in the therapy of psychiatric patients, toxic side effects were common. One of the most serious of these side effects has been orthostatic hypotension, which necessitated interruption or discontinuance of therapy in a number of cases. As the newer analogues have been developed, they have to a considerable extent replaced iproniazid as the agent of choice. Some investigators still prefer to use iproniazid, either specifically for its hypotensive effect, or in small amounts (10 to 50 mg. daily) which apparently are useful in antianginal prophylaxis.

Even small doses such as 10 mg. of iproniazid per day can relieve severity and frequency of anginal seizures and increase exercise tolerance up to 50 per cent within 1 to 2 weeks, according to Grauman,[49] who employed this small dosage successfully in treating 13 patients with severe to nearly intractable angina. All patients in this small series experienced mood elevation while on iproniazid; most striking antianginal benefits were achieved in those individuals in whom anxiety or a depressed state was an important feature. Master and Donoso,[37] too, found that many patients could be maintained on small doses.

Isocarboxazid

This preparation purportedly is 7 times as effective as iproniazid in inhibiting MAO in vitro and 8 times as potent in potentiating the central nervous system action of 5-hydroxytryptophane in mice. Its action is far more potent in the brain (33 times that of iproniazid) than in the heart (8 times that of iproniazid).[50] This increase in potency makes possible an average clinical dose of one quarter to one fifth that of iproniazid, and may be a factor in the reduction of frequency and severity of side effects reported with the newer preparation. We have employed 2 methods in administering isocarboxazid: in our younger and less seriously ill patients, we have started with the maximum dosage in order to reach full effectiveness within the shortest possible period; and we later have reduced dosage to the smallest amount that served to maintain the antianginal effect. In older and more seriously ill patients, we have administered smaller amounts and in divided doses. Although this might delay the energizing and antianginal effects of the drug, a wider margin of safety exists.

Over 70 per cent of our patients report appreciable benefit from isocarboxazid. We rarely have administered above 30 mg. per day: the majority of our patients have achieved maximum benefit with 15 to 30 mg. per day. This preparation has proved as effective as and frequently more effective than iproniazid, and sometimes is faster in onset of action.

Beta-phenylisopropylhydrazine

Eight times as potent in inhibiting MAO in vitro as iproniazid, beta-phenylisopropylhydrazine is 40 times as effective in vivo in inhibiting heart MAO and 43 times as effective as iproniazid in inhibiting brain MAO.[50] We have found isocarboxazid and beta-phenylisopropylhydrazine about equally effective in the prophylaxis of angina pectoris. Our customary procedure is to provide patients initially with 9 mg. of the preparation daily, in divided doses. In patients who receive complete relief of pain with this dosage, it later is reduced to 3 mg. twice daily. A reversible red-green color defect has been reported in a few patients on extended therapy with large doses of this agent.

Beta-phenylisopropylhydrazine has been used alone and in combination with chlorothiazide as an antihypertensive agent. As the MAO-inhibitors potentiate other hypotensive agents, lower doses of each are recommended.

Nialamide

This preparation is neither a stimulant nor a euphoriant. Nialamide has a relatively weak effect on brain MAO (about half the potency of iproniazid) and, perhaps for this reason, orthostatic hypotension has not been reported in clinical trials with this agent. As a rule, onset and development of the symptomatic effects are gradual. Wolffe and Shubin[42] report over 50 per cent improvement in 46 of 59 patients who received nialamide for the relief of angina pectoris, although 26 of these patients had had intractable angina or status anginosus prior to institution of the drug. Administered to patients with myxedema following I^{131} therapy, nialamide permits the use of sufficient thyroid to relieve hypothyroid symptoms to a considerable extent without reinducing severe angina; nevertheless, it has not been possible to administer sufficient thyroid to eliminate the myxedema completely without producing recurrence of the anginal attacks.[42]

Recommended initial dosage is 75 mg. of nialamide daily, in single or divided doses. After the first week, the daily dosage is revised upward or downward in steps of 12.5 or 25 mg., depending on the patient's tolerance. Once satisfactory response is obtained, dosage is reduced to the maintenance level.

Phenelzine (Beta-phenylethylhydrazine)

This potent, fast-acting MAO-inhibitor is reported to give good results in 80 to 85 per cent of patients with tension-fatigue states.[51] Kimbal et al.[52] reported that phenelzine markedly reduces the frequency and severity of migraine, and several investigators have found the drug to be of value in decreasing the number of attacks of angina pectoris. When given intravenously or intraduodenally to anesthetized dogs, phenelzine allegedly causes a marked increase in coronary blood flow with only minimal elevation of femoral arterial pressure. Dickel et al.[51] found that even in cases in which phenelzine had no antidepressant effect, the drug nonetheless substantially improved the patient's ability to profit by psychotherapy.

Side effects have been relatively minor, with no positive laboratory report nor clinical evidence of organ damage or blood dyscrasias in 580 patients.[53] Observed in only a few instances, orthostatic hypotension is most likely to occur in patients with low systolic pressures prior to therapy or in response to unusually large doses of the drug. The hypotension is not an indication for stopping therapy as it usually disappears within a few days or after reduction of dosage.[53]

The recommended starting dosage for most patients is 45 mg. daily, in 3 divided doses. If no response occurs within a week, an additional 15 to 30 mg. may be given at bedtime. After a maximal clinical effect is secured (1 to 3 weeks) the dosage is gradually reduced to a maintenance dosage of about 15 mg. daily or every other day.[53]

Side Effects

Reports of side effects during MAO-inhibitor therapy are frequent, but we must remember that in studies employing the double-blind technic, patients receiving placebo rather than MAO-inhibitor therapy also complain of headaches, dizziness, itching, nausea, weakness, tremors, diarrhea, and other untoward effects

The only significant side effect we have encountered among our patients has been the occurrence of severe orthostatic hypotension in several patients who were maintained on iproniazid. Where needed for immediate effect, methoxamine was administered. Under less severe circumstances cortisone or hydrocortisone (12.5 mg. 1 to 3 times daily) or ACTH in a slowly absorbed form has yielded good results. Slight hypotension may be controlled by the concomitant administration of amphetamine or amphetamine-like preparations. Orthostatic hypotension has not been noted in the patients we have treated with pivalylbenzhydrazine.

Agitation has not been a serious problem among our patients. If noted, agitation can be controlled by the concurrent administration of phenelthiazine, or a nonstimulating type of MAO-inhibitor may be substituted for the MAO-inhibitor in use (table 1).

Periorbital or dependent edema may occur but usually will subside even without diuretic therapy after the second or third week. For faster response, dosage can be reduced slightly or a diuretic may be employed. As chlorothiazide is potentiated by the MAO-inhibitors, we prefer to use organomercurials for this purpose except in the instances in which we seek the potentiation of chlorothiazide's antihypertensive effect.

Bladder or bowel dysfunction may be controlled by the administration of cholinergic stimulants, such as ambenonium or neostigmine. Hyperreflexia and hyperkinesis or muscle fasciculations are indications of excessive MAO-inhibitor dosage.

The administration of vitamin B_6 will prevent or correct instances of peripheral neuritis. We have not seen this side effect in our patients.

Both increases and decreases in sexual potency and activity have been noted under MAO-inhibitor therapy. Unless marked hypotension is present, alterations in sexual desires and activity usually disappear after a time without specific treatment.

Dietary precautions may be necessary to prevent unwelcome gain in weight. In some instances, the weight gain may be due to obstipation.

In the elderly patient especially, a sharp drop in systolic and diastolic blood pressure may result in decreased cardiac output with congestive failure and peripheral edema. Effects in these patients can be minimized by lowering the daily dose and administering the MAO-inhibitor in divided doses. Although this may delay energizing effects from 2 to 3 additional weeks, a wider margin of safety is provided by this practice.

Severe hepatitis has been reported to occur in patients undergoing iproniazid therapy, and a few instances of hepatitis have occurred in patients treated with the newer MAO-inhibitors. Although hepatitis probably will be extremely rare with the dosages now recommended, physicians must remember that these are potentially hepatotoxic materials and extreme caution must be exercised if they are employed together with other agents known or suspected to be hepatotoxic. We have had no instance of hepatitis or jaundice among our patients and attribute this in large measure to our continued alertness for signs or symptoms of impending toxicity or side effects of any sort.

Serial studies of hepatic function have occasionally yielded values outside the normal range, but no more frequently than similar values have appeared in tests of hepatic function in patients who are not on MAO-inhibitors. The abnormal values have without exception returned to within normal range during continued MAO-inhibitor therapy.

Conclusion

Development of the MAO-inhibitors unquestionably is an important forward step in the treatment of patients with angina pectoris. They also are useful in the treatment of hypertension. Provided patients are carefully observed for signs of any untoward effects and such tendencies are corrected immediately, side effects are exceedingly rare.

Summario in Interlingua

Le disveloppamento de inhibitores de monoaminoxydase es sin dubita un importante progresso in le

tractamento de patientes con angina de pectore. Tal inhibitores es etiam utile in le tractamento de hypertension. Providite que le patientes es meticulosemente observate pro signos de effectos adverse e providite que tal tendentias es corrigite immediatemente, effectos lateral es extrememente rar.

References

1. CESARMAN, T.: Serendipitia y angina de pecho. Informe preliminar sobre hallazgo terapeutico. Arch. inst. cardiol. Mexico **27:** 563, 1957.
2. BOSWORTH, D. M.: The use of iproniazid (Marsilid) in nontuberculous diseases. New York State J. Med. **58:** 3775, 1958.
3. WEISS, J., WEISS, S., AND WEISS, B.: Effects of iproniazid and similar compounds on the gastrointestinal tract. Ann. New York Acad. Sc. **80:** 854, 1959.
4. ROBIE, T. R.: Toxicity of aproniazid. *In* Correspondence. J.A.M.A. **168:** 1802, 1958.
5. ZELLER, E. A., BARSKY, J., AND BERMAN, E. R.: Amine Oxidases. XV. Inhibition of monoamine oxidase by 1-isonicotinyl-2-isopropylhydrazine. J. Biol. Chem. **214:** 267, 1955.
6. UDENFRIEND, S., WEISSBACH, H., AND BOGDANSKI, D. F.: Effect of iproniazid on serotonin metabolism *in vivo*. J. Pharmacol. & Exper. Therap. **120:** 255, 1957.
7. BOGDANSKI, D. F., PLETCHER, A., BRODIE, B. B., AND UDENFRIEND, S.: Identification and assay of serotonin in brain. J. Pharmacol. & Exper. Therap. **117:** 82, 1956.
8. FRIEND, D. G., ZILELI, M. S., HAMLIN, J. T. III, AND REUTTER, F. W.: The effect of iproniazid on the inactivation of norepinephrine in the human. J. Clin. & Exper. Psychopath., Suppl. 1, **6:** 61, 1958.
9. RESNICK, O.: The influence of amine oxidase inhibitors on epinephrine metabolism in man. Ann. New York Acad. Sc. **80:** 726, 1959.
10. HOFFER, A.: Relationship of iproniazid to epinephrine metabolism. Ann. New York Acad. Sc. **80:** 772, 1959.
11. JANTZ, H.: Zentr. ges Neurol. u Psychiat. 137: 141, 1956 (Quoted in Hoffer, A.: Relationship of iproniazid to epinephrine metabolism. Ann. New York Acad. Sc. **80:** 772, 1959.
12. BOGDANSKI, D. F., WEISSBACH, H., AND UDENFRIEND, S.: Pharmacological studies with the serotonin precursor, 5-hydroxytryptophan. J. Pharmacol. & Exper. Therapy **122:** 182, 1958.
13. SCHAYER, R. W.: *In vivo* inhibition of monoamine oxidase studied with radioactive tyramine. Proc. Soc. Exper. Biol & Med. **84:** 60, 1953.
14. OATES, J. A., AND ZALTZMAN, P.: In discussion following paper by Sjoerdsma et al. Ann. New York Acad. Sc. **80:** 977, 1959.
15. SCHALLEK, W.: Neurophysiological studies with monamine oxidase inhibitors. Dis. Nerv. System **21:** 64, 1960.
16. ALEXANDER, L., AND LIPSETT, S. R.: Effect of amine oxidase inhibitors on the conditional psychogalvanic reflex in man. Dis. Nerv. System **20:** 26, 1959.
17. BRODIE, B. B., AND SHORE, P. A.: A concept for a role of serotonin and norepinephrine as chemical mediators in the brain. Ann. New York Acad. Sc. **66:** 631, 1957.
18. SHOSHKES, M.: Discussion following Master & Donoso's paper. Ann. New York Acad. Sc. **80:** 1031, 1959.
19. EMELE, J. F., SHANAMAN, J. E., AND WARREN, M. R.: Analgesic activity of monamine oxidase inhibitors. Fed. Proc. **18:** 387, 1959.
20. RANDALL, L.: Toxicology of Marsilid. J. Clin. & Exper. Psychopath. Suppl. 1, **19:** 178, 1958.
21. GERTNER, S. B.: Monoamine oxidase inhibitors and ganglionic block. Fed. Proc. **18:** 393, 1959.
22. ZBINDEN, G., RANDALL, L. O., AND MOE, R. A.: Clinical and pharmacological considerations on the mode of action of monamine oxidase inhibitors. Dis. Nerv. System, Suppl., Sec. 2, **21:** 89, 1960.
23. ALLMARK, M. G., LU, F. C., CARMICHAEL, E., AND LAVALLEE, A.: Some pharmacological observations on isoniazid and iproniazid. Am. Rev. Tuberc. **68:** 199, 1953.
24. PLETSCHER, A., AND PELLMONT, B.: Biochemical and pharmacologic actions of Marsilid on the Heart. J. Clin. & Exper. Psychopath., Suppl. 1, **19:** 163, 1958.
25. PELLMONT, B., AND PLETSCHER, A.: Experimenteller Beitrag zur Wirkung von Isopropylisonicotinsaurehydrazid auf Herz und Kreislauf. Helv. Physiol. Acta. **16:** C25, 1958.
26. CRUMPTON, C. W., CASTILLO, C. A., ROWE, C. G., AND MAXWELL, G. M.: Serotonin and the dynamics of the heart. Ann. New York Acad. Sc. **80:** 960, 1959.
27. PLETSCHER, A.: Significance of monoamine oxidase inhibition for the pharmacological and clinical effects of hydrazine derivatives. Ann. New York Acad. Sc. **80:** 1039, 1959.
28. SCHWEIZER, W., AND VON PLANTA, P.: Ueber die Wirkung von Isopropyl-isonkinsaurehydrazid bei 100 Fallen von Angina Pectoris. Schweiz. med. Wchnschr. **88:** 882, 1958.
29. CRANE, G. E.: Clinical studies on the cardiovascular effects of Marsilid. To be published.
30. CESARMAN, T.: Iproniazid in cardiovascular therapy, with special reference to its action in angina pectoris and blood pressure. Ann. New York Acad. Sc. **80:** 988, 1959.
31. HARNES, J.: The effect of Marsilid on blood pressure in hypertensive patients. J. Clin. & Exper. Psychopath., Suppl. 1, **6:** 152, 1959.
32. NUSSBAUM, H. E.: Discussion following Harnes'

paper. J. Clin. & Exper. Psychopath., Suppl. 1, 6: 154, 1958.

34. ORVIS, H. H., AND TAMAGNA, I. G.: Iproniazid therapy of arterial hypertension. Clin. Research 7: 140, 1959.

35. MAXWELL, M. H.: Monoamine oxidase inhibitors in hypertension; a review. Paper presented at the Symposium on Amine Oxidase Inhibitors, Los Angeles, March 3, 1960.

36. GOLDMAN, D.: Clinical experience with newer antidepressant drugs and some related electroencephalographic observations. Ann. New York Acad. Sc. 80: 687, 1959.

36. SJOERDSMA, A., GILLESPIE, L., AND UDENFRIEND, S.: A method for measurement of monoamine oxidase inhibition in man; application to studies in hypertension. Ann. New York Acad. Sc. 80: 969, 1959.

37. MASTER, A. M., AND DONOSO, E.: Iproniazid in the anginal syndrome due to coronary disease. Ann. New York Acad. Sc. 80: 1020, 1959.

38. RIVIER, J. L.: In discussion following paper by Master and Donoso. Ann. New York Acad. Sc. 80: 1035, 1959.

39. COSSIO, P.: Contribution of iproniazid to the treatment of angina pectoris. Ann. New York Acad. Sc. 80: 1009, 1959.

40. MASTER, A.: Iproniazid (Marsilid) in angina pectoris. Am. Heart J., 56: 570, 1948.

41. SCHWEIZER, W.: Isopropylhydrazides in angina pectoris. Ann. New York Acad. Sc. 80: 1016, 1959.

42. WOLFFE, J. B., AND SHUBIN, H.: Treatment of angina pectoris with nialamide. Clin. Med. 6: 1563, 1959.

43. FISCHER, M. M., et al.: Isonicotinic acid hydrazide and its derivatives in tuberculosis; an evaluation of the side effects in relation to peripheral circulation. New York State J. Med. 52: 1519, 1952.

44. CASELLAS, A.: A new therapeutic drug (iproniazid) in angina pectoris. Bernat. M. Clin. 30: 322, 1958.

45. COSSIO, P.: The treatment of angina pectoris and other muscular pain due to ischemia with iproniazid and isoniazid. Am. Heart. J. 56: 113, 1958.

46. SCHERBEL, A. L., AND HARRISON, J. W.: The effects of iproniazid and other amine oxidase inhibitors in rheumatoid arthritis. Ann. New York Acad. Sc. 80: 820, 1959.

47. HOLTZ, P.: Ueber den gegenwartigen Stand der Serotonin. Forchung. Deutche med. Wchnschr. 83: 681, 1958.

48. REGELSON, W., HOFFMEISTER, F. S., AND WILKINS, H.: Effect of iproniazid on survival in the dog, following acute coronary occlusion. Ann. New York Acad. Sc. 80: 981, 1959.

49. GRAUMAN, S. J.: Small doses of iproniazid in the therapy of angina pectoris. Am. J. Cardiol. 3: 544, 1959.

50. ZBINDEN, G.: Clinical and pharmacological considerations on mode of action of monoamine oxidase inhibitors. Dis. Nerv. System, Suppl., 21: 89, 1960.

51. DICKEL, H. A., DIXON, H. H., SHANKLIN, J. G., AND DIXON, H. H., JR.: Tension fatigue states; treatment with phenelzine. Clin. Med. 6: 1579, 1959.

52. KIMBAL, R. W., et al.: Presentation before the American Academy of Neurology, April 18, 1959.

53. ARNOW, L. E.: Phenelzine; a therapeutic agent for mental depression. Clin. Med. 6: 1573, 1959.

Comprehensive Care of the Coronary Patient

A Challenge to the Physician

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THE MODERN physician should be able to secure a competent evaluation of his patient as a member of society, as an individual, and as a person with a physiologic disorder, in order to recognize the true extent of the disability and to provide appropriate, comprehensive care. In treating patients with coronary disease the physician's attention in the past has been properly fixed on assessing the anatomic injury and restoring physiologic function. This has been so because coronary heart disease inflicts its most obvious and immediate damage on the heart and its action. Today, however, as the clinical picture of coronary disease has developed more clearly, it has become increasingly evident that prognosis for life and even for return to pre-infarction cardiovascular function is better than was previously thought. Most patients survive the acute attack into the stage of convalescence. Here, the impact of this event on the patient's psychologic adjustment and on his place in the context of society thrusts itself on our attention. A man who has a heart attack is at least as likely to think of himself as a disabled breadwinner or as a frightened soul as to categorize himself as a coronary patient. The physician, on the other hand, is expected to have an intense preoccupation with his professional specialty and may, as a result, approach the patient's problem primarily on the level of "heart disease" when in fact the patient's major impairment may be recognizable only in the light of his social relationships, or of the psychic damage he has suffered.

This paper deals, therefore, with the impact of coronary disease on the social, psychologic, and physiologic balance of the individual, and is presented in 4 sections: (1) the coronary patient as a member of society, (2) the coronary patient as an individual, (3) impact of coronary disease on the physiologic balance of the individual, (4) clinical implications of comprehensive care.

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Supported in part by grants from the Cleveland Area Heart Society.

The Coronary Patient as a Member of Society

Coronary heart disease is a major social problem. Customarily our attention has been directed to cultural factors, such as diet, habits of activity, and genetic patterns, which contribute to the etiology of the disease. Today the time is appropriate to widen our viewpoint to include the even more impressive impact of the fully developed disease on society.

The United States of America leads the world in mortality from coronary heart disease, with an annual death rate of 829 per 100,000 in men aged 55 to 64.[1] The cardiovascular-renal diseases account for 55 per cent of deaths in this country. Coronary heart disease is the largest category within this group, and constitutes the majority of the 10 per cent of the living adults who are estimated to have heart disease. Mortality and morbidity increase rapidly above the age of 40, especially in men, with the result that coronary disease removes or disables the heads of many households, and thereby disrupts family and work situations. It looms over the middle-aged business executive and professional man as one of the most feared diseases, because of its supposed relation to the stress of modern working conditions. It has, in fact, afflicted many men in socially strategic roles, including the Presidency of the United States of America.

In an attempt to deal with some of these

effects, our society has developed a number of informally and formally institutionalized ways of dealing with coronary disease. Some are of positive value to the individual patient, whereas others are of doubtful value, or may even be clearly injurious.

Among informally agreed-upon patterns may be listed the attitudes of various social reference groups to which the patient belongs, such as co-workers, family, and fellow patients. Attitudes may differ widely, according to the orientation of the group. For example, the company for which the patient works may have a stringent retirement or rehiring policy that will inhibit his return to work. The patient's family may reinforce his fears, or, equally, give great encouragement to his hopes; or he may be powerfully influenced by the attitude of a physician who belongs to either the restrictive or the liberal "school" of treatment.

A second type of informal social pattern is the enlargement of the roles of physicians, nurses, social workers, and other health workers to include the function of "cardiac rehabilitation." This type of activity has, of course, always been implicit in what lay people expect of the medical profession, but it is noteworthy that the responsibility has become so much more specific as the dimensions of coronary disease have emerged.

A third informal social institution may be seen in the development of a socially legitimatized "coronary role" for the patient, one which is part of the general "sick role."[2] Such roles are most clearly seen in popular literature, because literature is a mirror reflecting the hopes and fears of its time. Significantly, the theme of coronary disease has appeared in advertisements, magazine articles, television programs, movies ("The Last Angry Man"), and even comic strips ("Rex Morgan, M.D."). A distinguished medical journal recently published a poem by a physician which epitomizes this view.[3]

Angina

Within the breast
Wherein each man must live
I bear the secret feel of death
The miniscule derivative of pain
That swells, and fills, and overflows
The arms, as of a spreading stain.
For as I talk, and laugh, and watch
The free and easy living of my peers,
How little do they make of what I know,
How all alone the heart, with all these fears.

I live sans exercise or toil,
Sans anger and without life's daily moil.
The nitrites add allegèd saving grace
To compensate for changes in my pace
Sometimes I wonder, after all is said and done,
Why don't I load the butter on my bun?
Drink champagne punch for breakfast, chase the girls?
Get roaring drunk, have several whirls,
Flit near the flame with Scotch, mid skols and skirls?
This greying reach of days, this flattened scene,
This uninspired vista of the years,
This living sine loving, sine strife,
Is for the birds; just ask my patient wife.

Outstanding among popular concepts of the coronary patient is the belief that the disease is connected ironically with excessive, self-driving ambition and that the attack—almost always grimly fatal—comes as a sort of punishment or divine warning (see *Thank God for My Heart Attack*).[4]

Inasmuch as the man susceptible to coronary disease is pictured as aggressively ambitious, there is emphasis on the attribute of the general sick role that is defined as "obligation to want to get well." This attribute has even led to a formalization of the coronary role in "Coronary Clubs," whose members meet to exchange experiences and derive courage from the association with others similarly afflicted, to live, to prosper, or even to diet "prudently." Such an institution has evident value for the coronary patient. It may, however, ritualize his separation and retard his return to the social pattern from which his disease initially set him apart.

"Coronary Clubs" are only one of several formal patterns that have been developed to deal with the social consequences of coronary disease. There are, for example, Workmen's Compensation rulings and legal precedents in personal injury cases, second injury laws, special laws, (such as the Utah Plan[5a]), special

insurance ratings, and, in the field of medicine, the development of the subspecialty of cardiac rehabilitation, with its experts, literature, task-oriented workshops, research, and Work Classification Clinics. Although each category cited is cast in a more or less formal legal or organizational code, none is rigid. Distinct changes are constantly evolving as our democratic society seeks more equitable solutions. The second injury law, for example, by absolving the employer from responsibility for medical conditions that developed prior to employment, protects him against some of the consequences of mounting compensation and personal injury awards. Similarly, the Utah Plan sets up a mechanism for bringing together and reconciling the often widely disparate medical and legal interpretations of specific cases involving disease or injury. The 48 Work Classification Clinics of the American Heart Association have a similar purpose and a common pattern of organization. They differ, however, in such details as source of financial support, eligibility, and the population served.

Almost every coronary patient comes in contact at some time with one of these formal social institutions, and this encounter may profit him financially or therapeutically. On the other hand, any formal institution shares with the "Coronary Clubs" the danger that it tends to perpetuate the coronary role beyond its appropriate limits. Where this danger is recognized and dealt with appropriately, as in the Work Classification Clinics, it is minimal. Where the system is not self-correcting, "compensationitis" may develop, and the motive to return to work may be quenched by the threatened loss of compensation income. By enlarging his view beyond the traditional focus on the patient alone, the physician learns how society deals with the legal, financial, and rehabilitation problems of his coronary patients. The more he comprehends their behavior, the better he can help them.

The Coronary Patient as an Individual

Coronary heart disease poses a major emotional problem to every patient. In fact, emotional reaction to coronary heart disease is as predictable and as characteristic as changes in the electrocardiogram or serum enzymes. The high incidence and prevalence of the disease alone are enough to invest it with fear. The symbolic importance of the heart, the "vital" organ, to a human being's sense of physical integrity has been recognized throughout recorded history, and it is no less precious and vulnerable today. The patient who suffers a myocardial infarction has to revise his image of himself in the presence of potential mortality. It has been the experience in Work Classification Clinics that the psychologic reactions of patients to this injury are prominent in almost every case and in many cases constitute the major disability.[5b]

Different human beings react differently to similar circumstances. Sex, age, social status, family background, and a unique set of personal experiences, all have their modifying effects on how a particular individual reacts to a major illness, such as myocardial infarction.

Lindeman has clearly identified a period of "grief work" through which a bereaved person must pass in order to adjust successfully to a loss.[6] Delay or avoidance of the grieving reaction tends to produce or perpetuate emotional disability. A psychologic study by Caron of patients with recent myocardial infarction showed that, after an initial period of denial of the significance of the illness, which was almost universal, the patients fell about equally into 2 main groups: those who continued to deny or minimize their illness, and those who recognized the seriousness of the situation and displayed distinctly depressive reactions.[7] A year later, the patients who had shown the depressive reaction were less disabled than those who continued to deny their illness. Thus, it appears that the concept of necessary "grief work" may have its parallel in the emotional adjustments of the patient with a myocardial infarct.

The period immediately following an illness as threatening as a myocardial infarction is certainly a time of emotional crisis. Major disturbances in the patient's relations with

other people have taken place, and he needs emotional support from any source, familiar or new, which he can tap. For many a coronary patient, the enforced passivity during the acute infarction may be especially distasteful and often unacceptable. Such a regimen is the antithesis of his usual self-sufficient, aggressive, dynamic, and driven personality. During the acute illness, the patient may have to "renounce ownership" of his own body, and passively permit himself to be handled. He is dressed and undressed, fed, cleaned, washed, helped with urination and defecation, turned from one side to the other; his nakedness is exposed to nurse and doctor, regardless of sex and of conventional decencies. He is, as it were, under orders, subjected to a hygienic routine that implies an unfeeling disregard for his personal attitude and preferences. Characteristically, many adults sum up this experience as "being treated as a baby," or as a "complete return to conditions of their childhood."[8] The discerning physician recognizes the way an individual patient meets the emotional crisis of a major illness and helps him face present and future medical realities, and finds outside help when needed, whether from family, friends, religious counselor, or psychiatrist. As Caplan has pointed out, the relationship between a family physician and his patient gives the physician particularly effective means to prevent emotional disability without undertaking deep, formal psychotherapy.[9]

Recent studies suggest that certain personality traits are more frequent among patients with coronary disease than among the general population. There is much evidence that men develop more coronary disease than women. The endomesomorph—the muscular, somewhat fat person—appears to be more prone to the disease than the ectomorph—the lean person.[10] These constitutional types are said to show certain characteristic personality traits. A recent Swedish study identifies the following 2 sets of characteristics as typical of the coronary patient: (1) "cyclothymous" temperament (warm, heavy, industrious, social, "viscerotonic"); and (2) "hysteroidous" temperament (agile, subjective, dramatic, egocentric).[11] Patients with coronary disease studied at the Cleveland Work Classification Clinic respond physiologically to standard psychologic testing and psychiatric interviewing in ways that are significantly different from the responses of an age-matched group of patients with rheumatic heart disease.[12] A group of men selected as manifesting an intense, sustained drive for achievement and as being continually involved in competition and deadlines had a much higher incidence of coronary disease than another group with opposite characteristics.[13] None of these studies proves decisively that personality is a primary factor in the etiology of coronary disease, but they do lend objective support to the clinical and popular impression of the coronary patient. A patient who shares some or all of these characteristics will receive therapeutic advice and approach his own rehabilitation in much the same way as he does other problems. The physician's task will be easier if he can recognize both typical and atypical features of his patient's behavior pattern and be prepared for a response similar to that which the patient has previously shown to other crises in his life.

Impact of Coronary Disease on the Physiologic Balance of the Individual

Reduction of coronary inflow produces significant physiologic effects in each individual that may be demonstrated with varying degrees of difficulty. Coronary disease has been called the "hidden disease" because of the obscure way in which it develops or manifests itself clinically. Approximately one fourth of the cases of myocardial infarct occur "silently."[5c] In such cases with unrecognized myocardial infarction or angina pectoris the physiologic effects may not be apparent; yet they are present in the form of vague somatic discomfort, easy fatigability, or reduced capacity to work to which the subject has adjusted without concern or awareness. In approximately 20 per cent of the cases the sole physiologic effect is sudden death. In the remaining majority of cases with overt coronary disease, the physiologic impact will

vary with the severity of the disease, the clinical course (angina pectoris, impending infarction, myocardial infarction, congestive failure), the effects of therapy, and the emotional reactions of the individual to the disease itself.

The Direct Effects of Coronary Disease on Cardiac Function

There is a surprising paucity of comprehensive studies of the effect of the various stages of coronary arteriosclerosis on cardiac function and fitness.[14] For example, little is known of the physiologic significance of the atherosclerosis found by Enos in 77 per cent of apparently healthy young men or of more advanced lesions in the same or similar populations.[15] As yet, no attempt has been made to relate the poor performance of fitness tests of American youths to the presence of such lesions.

With more advanced reduction of coronary inflow, clinical signs and symptoms may appear, accompanied by alterations of the contractile and electrical functions of the heart.

There is, however, a wide range of function at different times in the clinical course of patients with coronary artery disease.[14] The cardiac output has been reported as low or low normal during the acute phase of the infarction. After recovery, the resting cardiac output may not be significantly lower than that of control subjects of the same age. Measurements of cardiac output alone during exercise do not demonstrate difference between normal subjects and those patients with coronary disease who appear compensated clinically and who can perform the tests asymptomatically. However, differences in the oxygen uptake during exercise may distinguish these two groups. Physiologic studies have demonstrated the relatively good functional capacity of patients with a healed myocardial infarct. In asymptomatic patients, the changes in cardiac output, blood pressure, and circulation times during treadmill exercise (approximately 2 calories per minute) were indistinguishable from normal controls. Much more strenuous effort can be performed by some patients with a healed infarct. In a recent study patients surviving 1 to 5 years after infarction performed maximal sustained effort on a bicycle ergometer. One third of the patients had a maximal oxygen uptake in the normal range of 9 to 10 calories per minute, not much below that for untrained normal men. The others averaged 5 calories per minute, well above the usual 2 to 4 calories per minute energy expenditure required by most occupations.[14] In our own experience, about 55 per cent of patients with old myocardial infarcts were able to perform a 2-step test requiring an average of 480 Kg.M. per minute without symptoms or electrocardiographic changes.

The spectrum of function of coronary patients encompasses both those with angina decubitus and those with asymptomatic performance which approximates that of the normal subject and which may be distinguished from the strictly normal only by special high level tests.

Some aspects of the therapeutic regimen itself may exaggerate the physiologic significance of coronary disease, by their deleterious rather than beneficial effects. The continuation of a program of restricted physical activities long after the episode of acute infarction may perpetuate the ill effects of excessive bed rest. During World War II, Keys and his associates demonstrated that restrictive bed rest was associated with definite catabolic changes, loss of nitrogen, phosphorus, calcium, muscular wasting, decrease in skeletal muscle tone, bone atrophy, vasomotor instability, and decrease in cardiac output, blood volume, blood pressure, heart size, and exercise tolerance.[16] Healthy, normal, young soldiers required from 5 to 10 weeks to recover their tolerance to moderate exercise. Many such healthy subjects restricted to bed for a period of several weeks showed relative tachycardia at rest, and manifested signs of neurocirculatory asthenia on resuming physical activity, i.e., a relatively rapid heart rate, a feeling of faintness and dizziness, weakness, and anxiety. Coronary patients who have been excessively restricted

may also suffer similar ill effects of bed rest, and subsequent unfitness. In such cases the poor physical fitness induced by therapy may be difficult to distinguish from the effects of coronary disease per se on cardiovascular function.[14]

The emotional reactions of the patient to the advent of coronary disease may strongly influence his physiologic function. A significant role has been ascribed to emotions in the precipitation of one half of all cases of acute myocardial infarction.[17] The validity of this concept has not been established, although a great body of supportive evidence is currently accumulating. Emotional reactions or mental stress elevate blood fats (nonesterified fatty acids,[18] lipid mobilizing factor,[12] cholesterol,[5d] lipoprotein);[19] also, they increase the daytime production of epinephrine and norepinephrine;[20] they increase the systolic tension time index, i.e., myocardial oxygen consumption, independent of body oxygen consumption,[12] and possibly enhance blood clotting.[21] The etiologic role of emotions in producing myocardial infarction may be disputed; however, there is little reason to doubt that the emotional reactions of the coronary patient to his illness may have a significant effect on his heart function and work load during rest, especially if excursions of pulse rate and blood pressure are evoked by anxiety and frustrations.

The physiologic impact of coronary disease may persist, even after convalescence and restoration to usual activities and occupation. Apparently, coronary patients have a greater emotional reactivity than noncoronary patients. They show larger increments of cardiac output at rest and during anxiety,[22] wider excursions of blood pressure and heart rate, and more epinephrine production during the working day.[20]

The increased cardiac output and myocardial oxygen consumption during strong emotions may well act like that of thyrotoxicosis, anemia, or fever, and tax the heart and precipitate decompensation and chronic coronary insufficiency.[23]

Evaluation of Function and Physical Fitness of the Patient Recovering from Acute Myocardial Infarction

The responsible physician not only evaluates the organic defect, but also assesses competently the functional capacity of the patient with a physiologically disordered heart. Since the physiologic impact can vary so much, the functional capacity of each individual must be evaluated, not only from the very onset of the illness, but serially, through the acute illness, convalescence, and, thereafter, to detect changes in the course of the disease and the effects of treatment and of intercurrent diseases. In the past, functional capacity has been defined as "an estimate of what the patient's heart will allow him to do."[24] A more modern view holds that the clinical evaluation represents an expression of opinion concerning the functional capacity of the patient as modified directly or indirectly by his cardiac disease. The capacity of the coronary patient to perform satisfactorily certain muscular efforts (physical fitness), and also to have residual capacity to meet greater demands (reserve), may be affected not only by the direct effects of coronary arteriosclerosis and myocardial infarction and fibrosis, but also by lack of physical training, and by noncardiac factors, such as prolonged convalescence, loss of physical fitness due to restrictions, psychoneurosis, hyperventilation, acute infectious diseases, anemia, arthritis, age, pulmonary disease, and obesity (as mentioned above). In such cases the pertinence of these factors should be clearly recognized.

The clinical evaluation of cardiac capacity may be made more precise by careful history, relating signs and symptoms to the circumstances in which they develop, and to energy requirements of specific efforts. Inquiry into the response to activities of daily living yields valuable information regarding tolerance to effort. For example, how far can the patient walk?—or how many flights of stairs can he climb before noticing shortness of breath?—pain in the chest?—fatigue?—how long do these symptoms persist after such exertion? Are there contributing or modifying factors that

precipitate, modify, or aggravate discomfort?[5e] The physician may infer that there is a reduction of functional capacity when he obtains a history of easy fatigability, need for additional rest, usually recognized independently by the patient, self-imposed restriction of working hours, reduction of the pace of work, lengthening of rest pauses, and curtailment of usual recreational activities.

During the acute illness and convalescence, the physician makes a clinical appraisal of the changing fitness of patients from their tolerance to greater efforts. He can estimate the caloric level of the patients' fitness from the type of life activities performed without distress. The caloric load increases from approximately 1.25 calories per minute in basal activity (sitting, standing, talking, or lying down, i.e., slight physical activity); to 2.5 to 3.0 calories per minute to wash, shave, dress, drive a car; to 4.0 to 6.0 calories per minute to garden, to play golf, to walk briskly around the block, to climb stairs, to make beds, to scrub floors, i.e., moderate to severe exertion.[25]

The historical method provides a preponderantly subjective measure of function and physical fitness, but may be obscured by the patient's psychologic responses, work motivation, social pressures, pain threshold, or need to deny pain. Nevertheless, correlations between clinical evaluations, employing the classification of the New York Heart Association, and objective functional testing have been good in 70 to 84 per cent of the cases.[26] Factors that reduce the accuracy of the clinical impression have been unsatisfactory history, failure to evaluate the patient's emotional status, excessive limitation of physical activity by the patient or the physician, recent convalescence or other disease, or concurrent drug therapy. Despite these limitations, wider use of the New York Heart Association classification has been advocated because it is correlated not only with physical fitness, but also with on-the-job work capacity and with prognosis.[14]

Although these correlations do exist, objective functional measurement still may be needed to evaluate the cardiac reserve of the individual patient. Evaluation by laboratory testing may be redundant for patients at the opposite ends of the clinical spectrum. The majority of coronary patients, however, lie between these extremes, with intermediate degrees of impairment. It is this group that "taxes the cardiologist's skill in defining their status properly from a clinical basis alone."[2]

Just as the historical method of estimating cardiac function has limitations, so estimating heart size is of limited value as a measure of function. The importance of determining the size and shape of the heart has been highlighted by recent researches that confirm older observations: viz., the oxygen requirement of the heart is determined by its diastolic size, as expected from the law of LaPlace.[5f] Furthermore, the same intraventricular tension-time index (i.e., mean systolic pressure times duration of systole) will require a greater myocardial fiber tension in a large heart than in a small one.[5g] In other words, since tension-time index is the principal, if not the sole determinant of myocardial oxygen utilization,[5h] the large heart consumes more oxygen to develop the same intraventricular tension-time index. The large or dilating heart "may be thought of as one with an O_2 requirement that approaches or finally could exceed the limit of the O_2 available to it, especially when O_2 availability is limited by disease,"[5g] as by coronary disease. Heart size is significant in approximating reserve of patients with coronary artery disease, cardiac enlargement, and congestive failure, but is limited in coronary patients with normal size or small hearts whose function is restricted by angina rather than by myocardial insufficiency, i.e., power failure, and in patients with localized enlargement due to ventricular aneurysm formation. The performance of the latter may be remarkably good.

Since there are no methods currently available that predict performance on the basis of measurements made at rest (particularly disappointing is the ballistocardiogram), effort tests have been developed and widely used by clinicians. Generally, they involve the use of large muscle masses, require no special

training or motivation, and have realistic energy requirements comparable to that of contemplated work activities. The prolonged tests (such as treadmill, bicycle ergometer) and the brief step tests (Master, Åstrand, Cureton, Nylin, etc.) afford a good basis for the evaluation of the circulatory function and fitness for steady state and peak efforts requiring approximately 5.0 to 6.0 and 8.0 calories per minute.[14] At the present time, except in experimental studies, the use of steady-state maximal work tests (10 to 20 calories per minute) for cardiac patients seems inadvisable, since so few occupations require this much effort. Even the submaximal work steady-state tests, such as Åstrand's, in which an oxygen intake of 2 liters per minute occurs, may be excessive.[14]

The need to know the tolerance of the cardiac to both peak and steady-state efforts has been indicated by recent observations on-the-job of such subjects, as well as of normal workers. It is usually peak effort and not sustained effort that is the limiting factor in determining the suitability of a job. Dock workers[27] and steel mill workers[28] perform high energy efforts in spurts of approximately 1.5 to 2.0 minutes, followed by periods of rest of equal duration. In the factory, lower levels of energy are sustained for somewhat longer periods, interspersed with rest periods which amount to 65 per cent of the work shift.[29]

The physician will find exercise tests more valuable if he knows their physiologic cost and evaluates the physiologic response in terms of multiple parameters, rather than solely by the electrocardiogram. The most informative parameters include heart rate, blood pressure, electrocardiogram, cardiac output, as approximated by pulse pressure methods or other methods, estimated myocardial oxygen consumption from tension-time index, and the recovery of these parameters after the cessation of exercise. Burton and others have reaffirmed the value of the heart rate as an index of the stress on the heart. An increase in heart rate increases the tension time and is probably better than the work alone as an indication of total energy requirements.[51] Other parameters include respiratory rate, oxygen debt, and blood lactate and pyruvate as measures of the degree of anaerobic energy liberation. This concept of characterizing the heart in terms of multiple parameters analogizes it with a complex motor whose dysfunction can be manifested by changes in mechanical and electrical adequacy and changes in their coupling. Thus, there can be power, i.e., muscular failure (inadequate cardiac output), valvular failure, coronary failure, and electrical failure (mechanism, conduction), as well as combinations thereof.

In evaluating the response of the coronary patient to exercise tests, the physician should recall that the primary purpose of the test is the assessment of exercise tolerance. Exercise tests do not establish a diagnosis of coronary insufficiency or myocardial ischemia. In fact, none of the exercise tests is specifically diagnostic of coronary artery disease. Neither abnormal electrocardiographic changes nor abnormal physiologic responses (delayed fall of blood pressure after exercise and low ratio of oxygen consumption during exercise to oxygen debt) are specific for coronary artery disease, since they occur with almost equal frequency in patients with hypertensive cardiovascular disease, in those with rheumatic heart disease, and to a lesser extent in otherwise normal subjects.[25] Additional information often is required to determine whether the response to exercise is due to the heart disease per se, lack of previous training, loss of fitness, anxiety, or age. Thus, critical rationalization of function is more meaningful, albeit more difficult, than its assessment alone.

Enhancement of Cardiac Function and Fitness of the Coronary Patient

Currently a new concept is emerging that circulatory function of the cardiac patient as well as that of the normal individual may be enhanced not only by conventional treatment (weight reduction, early ambulation, drugs, relief of anxiety) but also by deliberate training. This concept has developed from the experiences of work and sports physiologists who have demonstrated unequivocally that

physical fitness can be enhanced by training in the fit and unfit "healthy" subjects. Fit individuals show (a) less cardiac acceleration and lower systolic pressure, (b) larger stroke volume, (c) lower blood lactate, (d) lower systolic tension time, equivalent to lower myocardial oxygen requirement, and (e) lower oxygen consumption, implying higher external and possibly higher internal efficiency.[5g] Arterial pressure and pulse rate also return more rapidly to resting levels after completion of the work. The fit person shows (a) longer endurance before exhaustion, (b) higher oxygen consumption, (c) less increase in heart rate, and a lower maximal rate, (d) larger stroke volume, (e) higher blood lactate, and (f) a more rapid return of arterial pressure and heart rate to pre-exercise levels.[30]

In addition, clinical and experimental evidence is accumulating which emphasizes the value of physical fitness in normal subjects and patients with heart disease, and in experimental animals. Sustained physical conditioning is reported to be associated (a) with greater longevity, (b) with a lower general mortality rate (skiers,[5j] farmers,[5k] tram conductors,[31]), (c) with a lower morbidity and lower mortality in physically active patients with coronary disease than in those who are inactive, (d) with slower pulse rates during performance of emotionally charged and low caloric body work,[12] (e) with enhanced development of intercoronary collateral circulation (Eckstein), and (f) with lesser atherosclerosis in cholesterol-fed animals (Kobernick).[14] Furthermore, the ill effects of "loafing"[32] and the beneficial effects of work on physical fitness have been recently emphasized.[14]

The experiences gained in the training of normal subjects are now being applied cautiously to the problems of the patient with cardiac disease. The work performance of patients with neurocirculatory asthenia has been improved by training, with resultant slower resting and work pulses, and restoration of peripheral A-V oxygen extraction to normal levels.[33] Cureton has reported that several cardiac patients showed smaller hearts after a training program.[34] In regard to the coronary patient, although prophylactic training programs have been widely heralded, they have had a limited therapeutic application after the disease has appeared. It is obviously desirable to enable the coronary patient to obtain the possible benefits of training, particularly reduction of systolic tension time, which would be anticipated on the basis of the effects of training of normal subjects.

Encouragement to initiate training programs of coronary patients has been derived chiefly from the remarkable results of early ambulation, and the experiences of Work Classification Clinics and industrial physicians which demonstrated that coronary patients can work safely and successfully in a wide range of jobs with high and low caloric and environmental requirements, and that work capacity of the cardiac can improve during employment.[5l] At a recent conference on exercise two groups of investigators presented favorable reports on their preliminary experiences with progressive exercise of patients with old (more than 3 months) myocardial infarcts.[35] Precautionary measures during exercises included strict monitoring of multiple physiologic parameters. The principles of physical training developed by sports physiologists were employed, including progressive loading and adequate periods for recovery.

The objective improvement of physical fitness of individual coronary patients after progressive training was striking. In selected instances, the trained coronary patients were more fit than so-called normal persons, fit or unfit. One noteworthy case, a trained 64-year-old man with an old anterolateral myocardial infarct and left bundle-branch block ran 10 miles in 77 minutes. At a later date he performed steady-state exercise on a bicycle ergometer at 900 Kg.M. per minute with slower pulse rates than those reported for normal subjects of similar age.[12]

For the present time, the practicing physician may look askance at these efforts to train coronary patients, although he may be in accord with the view of Diem that "what is good for the organs of Zatopek, for the vessels

and the musculature of an Olympic champion, surely ought to be beneficial for those of a body weakling, individually prescribed and adapted . . . .''[36] The results of current and future studies may yield practical information whether the individual patient can train his heart without the risk of untoward effects, and without cumbersome laboratory monitoring; and whether and when systematic rest is to be preferred to training.[5m] Also it is important to learn whether a cardiac patient can train his peripheral structures and thus relieve the burden upon his heart.[5m] In the meanwhile, the practicing physician should feel encouraged to liberalize commonly imposed physical restrictions and encourage the individual patient to improve his physical fitness judiciously and progressively.

Clinical Implications of Comprehensive Care

However skillfully the sociologist, the psychologist, and the physiologist dissect him, the patient stubbornly remains an intact human being, struggling back toward homeostasis with all the forces he can muster. The practicing physician can help the patient to recognize his needs in the most important categories, to measure his resources, and to obtain help. These 3 functions, consistently performed and flexibly adapted as long as problems related to the illness persist, constitute comprehensive care.

First, the physician must define the patient's needs and resources. Most of the necessary data can be collected by means of the medical history and physical examination. The primary objective in traditional history-taking has been to help establish a diagnosis. Another objective, and one less frequently emphasized in the past, is the evaluation of physiologic reserve. It is this kind of history-taking, relating symptoms to activity, to emotional events, and to response to therapy, that provides the basic data for rehabilitation. In order to make a meaningful estimate of functional capacity, the practicing physician should have a working knowledge of the energy requirements of common activities, of the physiologic effects of bed rest and ordinary drugs, and of the practical aspects of the physiology and psychology of work.[37–39] He should be aware of the many important interrelationships between the coronary disease and the patient's emotional and social life. For the coronary patient, most of this information can be coded conveniently in the diagnostic, functional, and therapeutic classification of the New York State Heart Association. Diagnosis and the delineation of a patient's physiologic reserve can usually be established adequately by questioning, but it may sometimes be necessary to supplement this with exercise tests and on-the-job observations.[28, 29] The application of laboratory measures becomes more meaningful if related to the physical and emotional requirements of the world in which the patient lives, works, and plays. Work Classification Clinics are now available to the physician and his patient in many cities for consultation and special testing.

The patient with established coronary disease invariably has needs and depleted reserves in the psychologic and social spheres, as well as in his biologic functioning. He brings them as part of his medical problem into the physician's office or the hospital. The modern clinician must be alert to these problems, not because he is expected to solve them single-handedly, but because they seriously interfere with restoration to physical health. Emotional reactions are as integral a part of coronary disease as the organic lesion. They must be actively anticipated, coped with, or when possible, prevented throughout the entire illness.

Unfortunately, human needs and resources of this type are less readily measurable and classifiable than their physiologic counterparts, though this fact does not diminish their importance. A revision of standard classification is being undertaken by the American Heart Association, and it may be possible to introduce uniform descriptions in these areas soon. Meanwhile, the physician can increase his own effectiveness by being sure to include in his customary medical history an assessment of the patient's social situation (family,

sexual, vocational, educational, and economic status), personality traits, and characteristic emotional patterns. The physician should take into account the effects the illness has had on each. The aim of the practicing physician should be to construct a multidimensional picture of his patient; no single frame of reference alone can adequately represent the sick person and reveal what, for him, are the real problems connected with his disease. The individual practicing physician is often the only person who is able to take a truly comprehensive view.

Once the needs of the patient are recognized, means must be found to meet them. The first step is to develop an organized, specific plan of treatment. Drugs must be prescribed judiciously, with thought for their cost, ease of administration, and hazards. Advice concerning diet and activity must take into consideration the patient's personal and cultural habits and preferences, and recognize what it means to him to be deprived of familiar foods and activities. Every mode of treatment must be undertaken prudently, weighing its proved value for treatment and prevention against its inconveniences and dangers. Similar restraint and sound judgment also are needed in the counseling and prescription of prophylactic programs to modify coronary atherosclerosis in members of the patient's family.

When it comes to filling social and emotional needs, however, the physician's role changes from that of a diagnostician-therapist to that of a diagnostician-planner. The same orderly thought process that derives a diagnosis and therapeutic plan from the data of the history and physical examination can also define the patient's social and psychologic problems and point to the most effective solutions. But here it becomes crucial for the physician to recognize that the limits of his professional skill do not necessarily coincide with the extent of the needs related to this particular illness. If he recognizes both his own limitations and the variety of the patient's difficulties, he will welcome the assistance of the patient's family and friends and of specialists in psychiatry, social work, or vocational counseling. When a physician turns to others for appropriate help in managing problems in which he is not highly skilled, he does not restrict his role or abdicate his authority; rather, he makes it clear to the patient that he remains in a central position as guide and counselor, seeing the problem whole, rendering the kind of help he is trained to give, and delegating that for which others have more time and training.

The first step toward meeting these diverse needs is to establish and maintain good communications with the patient and the key people who can help him regain his equilibrium. Unless the patient's family and employer have some understanding of his capacities and progress, the physician's plan for treatment may be thwarted. As the patient moves from the acute illness through convalescence and rehabilitation, there is a change in the importance and usefulness of various health personnel. At first the nurse has a more important role, and, later, the social worker and vocational counselor; the family is always important. It is often only through them that diet, weight, and physical activity can be regulated. Needs change, and the patient's reaction to his disease changes. Periodic review of the whole situation makes possible a flexible, dynamic plan of action that conforms to the progress of physiologic, psychologic, and social rehabilitation.

These three aspects derived from physiology, psychiatry, and sociology, outline our present concept of rehabilitation. This concept offers a challenge to the traditional orientation of the medical practitioner. Diagnosis and specific therapy should be supplemented by knowledgeable counsel regarding the many aspects of life that are touched by coronary disease. If the practicing physician is to retain his central role in the provision of health care for the patient with coronary disease, he should develop competence in work physiology and work together with the growing corps of allied professional health workers. By thus seeking with his patients the appropriate responses to all the major perturbations of dis-

ease, he will reaffirm the classic purpose of medicine: to help sick people find their way back to integrity of body, mind, and spirit.

Summario in Interlingua

Le presente reporto concerne le impacto de morbo coronari super le balancia social, psychologic, e physiologic del individuo e es organisate in 4 sectiones: (1) Le patiente coronari como membro del societate; (2) le patiente coronari como individuo; (3) le impacto de morbo coronari super le balancia physiologic del individuo; e (4) le inherentias clinic del concepto de assistentia total.

References

1. YUDKIN, J.: The epidemiology of coronary disease. Progr. Cardiovas. Dis. **1**: 116, 1958.
2. PARSONS, T.: Social structure and dynamic process: the case of modern medical practice. *In* The Social System. Glencoe, Ill., Free Press, 1951, Chap. X.
3. STOREY, D.: Angina. New England J. Med. **261**: 1282, 1959.
4. HARRISON, C. Y.: Thank God for My Heart Attack. New York, Henry Holt, 1949.
5. ROSENBAUM, F. F., AND BELKNAP, E. L.: Work and the Heart, New York, Paul B. Hoeber, 1959. 5a, p. 482; 5b, p. 335; 5c, p. 272; 5d, p. 168; 5e, p. 141; 5f, p. 74; 5g, p. 31; 5h, p. 30; 5i, p. 75; 5j, p. 200; 5k, p. 118; 5l, p. 337; 5m, p. 209.
6. LINDEMANN, E.: Symptomatology and management of acute grief. Am. J. Psychiat. **101**: 141, 1944.
7. CARON, H.: The crisis factor in illness. Cleveland Symposium on Research on Psycho-Social-Vocational Aspects of Physical Disability, Highland View Hospital, November 4, 1959.
8. FREUD, A.: Lecture: Role of bodily illness in mental life of child. Psychoanalyt. Study of the Child **7**: 71, 1952.
9. CAPLAN, G.: Practical steps for the family physician in the prevention of emotional disorder. J.A.M.A. **170**: 1497, 1959.
10. GERTLER, M. M., AND WHITE, P. D.: Coronary Heart Disease in Young Adults: A Multidisciplinary Study. Cambridge, Mass., Harvard University Press, 1954.
11. FORSSMAN, O., AND LINDEGARD, B.: The postcoronary patient. J. Psychosom. Res. **3**: 89, 1958.
12. HELLERSTEIN, H. K.: Unpublished observations.
13. FRIEDMAN, M., AND ROSENMAN, R. H.: Association of specific overt behavior pattern with blood and cardiovascular findings. J.A.M.A. **169**: 1286, 1959.
14. TURELL, D. J., AND HELLERSTEIN, H. K.: Evaluation of cardiac function in relation to specific physical activities following recovery from acute myocardial infarction. Progr. Cardiovas. Dis. **1**: 237, 1958.
15. ENOS, W. F., HOLMES, R. H., AND BEYER, J.: Coronary disease among United States soldiers killed in action in Korea. J.A.M.A. **152**: 1090, 1953.
16. KEYS, A.: Deconditioning and reconditioning in convalescence. S. Clin. North America **25**: 442, 1945.
17. DREYFUSS, F.: Role of emotional stress preceding coronary occlusion. Am. J. Cardiol. **3**: 590, 1959.
18. BOGODONOFF, M. D., WEISSLER, A. M., MERRITT, F. L., HARLAN, W. R., AND ESTES, E. H., JR.: The role of the autonomic nervous system in human lipid metabolism. Fifty-First Annual Meeting of the American Society for Clinical Investigation, Atlantic City, N. J., May 4, 1959.
19. GRUNDY, S. M., AND GRIFFIN, A. C.: Relationship of periodic mental stress to serum lipoprotein and cholesterol levels. J.A.M.A. **171**: 1794, 1959.
20. FRIEDMAN, M., ST. GEORGE, S. M., BYERS, S. O., AND ROSENMAN, R. H.: Excretion of epinephrine, norepinephrine, and other hormones in men exhibiting a behavior pattern (A) associated with coronary artery disease. Circulation **20**: 698, 1959.
21. —, ROSENMAN, R. H., AND CARROLL, V.: Changes in serum cholesterol and blood clotting time in men subjected to cyclic variation of occupational stress. Circulation **17**: 852, 1958.
22. STEVENSON, I. P., DUNCAN, C. H., AND WOLFF, H. G.: Circulatory dynamics before and after exercise in subjects with and without structural heart disease during anxiety and relaxation. J. Clin. Invest. **28**: 1535, 1949.
23. NEU, H. N.: Rehabilitation of the cardiac patient, Geriatrics **13**: 640, 1958.
24. Criteria Committee: The New York Heart Association Nomenclature and Criteria for the Diagnosis of Diseases of the Heart and Blood Vessels, Ed. 5. New York, New York Heart Assn., 1953.
25. HELLERSTEIN, H. K., AND FORD, A. B.: Rehabilitation of the cardiac patient. J.A.M.A. **164**: 225, 1957.
26. BRUCE, R. A.: Evaluation of functional capacity in patients with cardiovascular disease. Geriatrics **12**: 317, 1957.
27. HALE, F. C., AND O'HARA, J. J.: Energy Expenditure of Longshoremen. University of California, Los Angeles, Cal., Report No. 59-20, June, 1959.
28. FORD, A. B., HELLERSTEIN, H. K., AND TURELL, D. J.: Work and heart disease II. A physiologic study in a steel mill. Circulation **20**: 537, 1959.
29. —, AND —: Work and heart disease I. A physiologic study in the factory. Circulation **18**: 823, 1958.

30. WIGGERS, C. J.: Physiology in Health and Disease, Ed. 5. Philadelphia, Lea & Febiger, 1949.
31. MORRIS, J. N., HEADY, J. A., RAFFLE, P. A. B., ROBERTS, C. G., AND PARKS, J. W.: Coronary heart disease and physical activity of work—evidence of a national necropsy survey. Brit. M. J. 2: 1485, 1958.
32. RAAB, W.: Das Faulengerherz: die pathogentische Bedeutung Körperlicher Untätigkeit. Wein. klin. Wchnschr. 70: 709, 1958.
33. SJOSTRAND, T.: Vasoregulative asthenia therapy by physical training. Aerztl. Forsch. 12: 425, 1958.
34. CURETON, T. K.: Shrinkage of the heart size associated with improved cardiovascular condition due to progressive physical training of three middle aged men. J. A. Phys. Ment. Rehab. 10: 75, 1956.
35. HAFKENSCHIEL, J., AND HELLERSTEIN, H. K.: Discussions in the Seminar on the Electrocardiographic Exercise Test, Burlington, Vt., September 19-20, 1959.
36. HOLLMAN, W.: Der Arbeits-und Trainingseinfluss auf Kreislauf und Atmung, Darmstadt, Germany, Dietrich Steinkopff, 1959.
37. LEHMANN, G.: Praktische Arbeitsphysiologie, Stuttgart, Germany, Georg Thieme, 1953.
38. PASSMORE, R., AND DURNIN, J. V. G. A.: Human energy expenditure. Physiol. Rev. 35: 801, 1955.
39. ERIKSON, E. H.: Young Man Luther. A Study in Psychoanalysis and History. New York, W. W. Norton, 1958.

Now, I happen to be convinced that variety is much more than the spice of life: variety comes very near to being the most reliable guarantee of survival that we possess. Life is forever trying new combinations, different arrangements, various experiments.—ALAN GREGG, M.D. *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 95.

CLINICAL PROGRESS

Russian Research on the Role of Visceral Reflexes in Coronary Insufficiency

By ERNST SIMONSON, M.D.

THE ROLE of the central nervous system in the pathogenesis of cardiovascular disease has been emphasized in the Russian literature.[1] This concept is perhaps most pronounced in their research on arterial hypertension,[2] but is applied also to coronary artery disease, and particularly to angina pectoris.[3, 4]

The large experimental and clinical material accumulated in the past decade by Russian authors cannot be reviewed in detail in this article. A few representative references, however, are given as general background for the main topic: the effect of reflexes from gastrointestinal receptors on coronary insufficiency. In prolonged experimental neurosis in monkeys, produced by conflicting conditioned reflexes, in some of the animals electrocardiographic changes developed that were identical to those of human left ventricular ischemia. Apparent angina attacks developed, and one monkey died of myocardial infarction, confirmed by autopsy.[5] Vovsi[6] found pronounced changes of the electroencephalogram in 30 patients with coronary artery disease during attacks of angina pectoris, together with typical S-T depression in the electrocardiogram. Zamislova and Bodnar[7] reported a higher incidence of disturbance in the electroencephalogram and other central nervous system functions in 58 patients with coronary heart disease than in healthy subjects. Gukasyan and Tapitser[8] stressed the role of the central nervous system in the development of myocardial infarction on the basis of clinical impression. Since central nervous system effects on the heart have to be mediated through the autonomic nervous system, effects of stimulation of autonomic centers, vagal, sympathetic, and cardiac nerves on coronary circulation have been studied on a rather large scale. Ligature of one branch of the left coronary artery produces spasm in other branches, which can be abolished by bilateral vagosympathetic block.[9] After ligation of the anterior descending branch of the left coronary artery in dogs the majority of animals did not develop myocardial infarction, but vagal stimulation after ligature produced infarction.[10]

Similar results were obtained by Kuzmina-Prigradova.[11] Vagal stimulation immediately after ligation of the anterior descending branch of the left coronary artery in dogs, and even 2 to 3 days later, increased the size of the infarct together with hemorrhages and edema. Infarction after ligation of this artery could be prevented in 8 of 10 animals (monkeys, dogs, cats) by local anesthesia of the arterial wall, at the site of the ligature, with 5 per cent cocaine or 2 per cent procaine, whereas in all 9 control animals (without local anesthesia) myocardial infarction developed.[12] Chronic vagal stimulation accelerated the development of electrocardiographic abnormalities in rabbits and experimental atherosclerosis produced by cholesterol feeding.[13]

These results have found therapeutic application in the treatment of patients with coro-

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Supported by grant T3 (C2), National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

nary heart disease by means of procaine block in the substernal mediastinum. Ostapiuk[14] injected 60 to 80 ml. of 0.5 per cent procaine solution in 55 patients, in intervals from daily to weekly (total of 320 injections). This procedure stopped anginal attacks in 32 patients after the second injection, and in 9 there was a reduction in the frequency and severity of the attacks. Exercise tolerance increased in most patients. The electrocardiogram improved in 20 patients (disappearance of ventricular extrasystoles, less pronounced S-T depression and T inversion). Side effects of the injection (general weakness and vertigo) disappear usually after 15 to 45 minutes, but were more prolonged and severe in 5 patients. The author considered blood pressure over 200/110 or below 90/50 a contraindication to this technic. The favorable results of repeated intrathoracic procaine block were confirmed by Bulatov and Stukkei,[15] who used for the first injection 60 to 80 ml., and for subsequent injections 100 to 120 ml. of 0.5 per cent procaine solution. No complications occurred in 219 injections in 88 patients. Only 19 patients did not show any improvement; in 36, the results were excellent (disappearance of effort angina), and a moderate improvement was noted in 33 patients. In a follow-up study of 30 patients the absence of anginal attacks lasted from 6 to 12 months in 13; from 1 to 2 years in 5; and over 2 years in 8.

These results may be considered as a basis for studies on reflex effects of stimulation of visceral receptors on coronary circulation. A variety of visceral receptors was studied, but the effect of the stimulation of gastrointestinal receptors appears to be the most important in view of the known relationship between gastrointestinal symptoms and coronary insufficiency or myocardial infarction. The previous experimental work seems to have been limited to the effect of mechanical stimulation of gastrointestinal receptors on coronary circulation.

Gastric distention produced in dogs a reflex constriction of the coronary arteries.[16] This was confirmed by Gilbert, Fenn, and LeRoy,[17] who measured the flow in the circumflex branch of the left coronary artery by means of a thermostromuhr after the chest was closed. A decrease of the coronary blood flow occurred in 8 of 12 animals, and was prevented by atropine.

One of the most thorough investigations on the effect of gastrointestinal stimulation has been performed by I. E. Ganelina over the past 5 years. Ganelina also started with the effect of mechanical stimulation, but rather than direct measurement of the coronary flow, electrocardiographic changes were used as criteria. Electrocardiographic changes are less specific than measurement of coronary blood flow, but have the advantage of easier application, facilitating experiments on animals on a large scale and application to man. Inflation of ligated intestinal loops up to a pressure of 40 to 80 mm. Hg produced no or only minor electrocardiographic changes in 11 normal rabbits, whereas in 9 of 40 rabbits with experimental cardiovascular pathology (arterial hypertension produced by deafferentiation, atherosclerosis produced by cholesterol feeding) pronounced electrocardiographic changes occurred (mostly T inversion). Fig. 1 shows one example from Ganelina's experiments.[18] Ganelina extended her work to chemical stimulation, which has not been studied before, and has pertinent clinical applications.

Chemical stimulation[19, 20] of perfused, isolated intestinal loops in situ with intact innervation with 10 to 50 gamma of acetylcholine produced in 36 normal anesthetized cats no electrocardiographic changes or a small variation of the T wave, not exceeding 1 mm. In contrast, pronounced electrocardiographic changes (abnormal T inversion, reversal of an inverted T, or ventricular bigeminy) developed in 12 of 25 cats with experimental myocarditis, produced by repeated intravenous injection of caffeine benzoate and epinephrine. The myocarditis was confirmed by autopsy. The electrocardiographic changes were prevented by prior denervation of the intestinal loop or by topical procaine application (fig. 2). It is of great interest that the heart was sensitized to mechanical or chemical stimulation of visceral receptors by cardiac pathology.

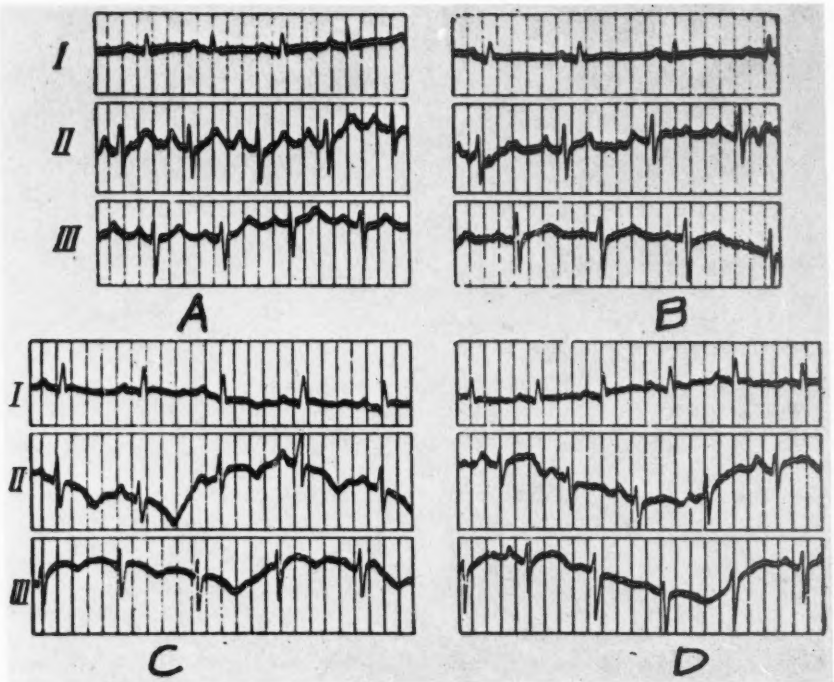

Figure 1

Electrocardiogram of a rabbit with experimental arterial hypertension and atherosclerosis. A, *before the experiment;* B, *after preparation of the intestinal loop (ligation)—no essential changes;* C, *during inflation of the intestinal loop (80 mm. Hg.)—T wave inversion in leads II and III;* D, *5 minutes after release of inflation pressure—T_2 and T_3 small positive, but still smaller than in "B". (Reproduced from Ganelina,[18] figure 1).*

Increased sensitivity of the heart to acetycholine stimulation of the isolated intestinal loop in situ was also shown in 7 of 11 cats with intestinal obstruction (S-T depression, flattening or inversion of T).[21] In 2 dogs with experimental hypercholesteremia and probably early atherosclerosis produced by cholesterol feeding and methylthiouracil over a period of several months, chemical stimulation (1/4 per cent M HCl) of an intestinal loop through a fistula produced partial inversion of T_2. No inversion of T_2 occurred in the same dogs before hypercholesteremia.[22]

Oral application of mustard in a starch capsule produced comparatively small changes of the electrocardiogram in about half of 50 healthy subjects and pronounced changes in 22 of 33 patients with coronary disease.[22] The subdivision of "small" and "large" changes was arbitrary. The "large" changes include P-R prolongation over 0.04 second, changes of T in 2 or more leads over 0.5 to 0.75 mm., or S-T displacement (critical values are not given). These criteria are fairly liberal.[23] The example of "large" changes in a patient with coronary heart disease (fig. 3), however, is not impressive in comparison with a positive exercise or hypoxemia test (of which Ganelina is aware), or with an abnormal meal test.[24] Ganelina's material was later enlarged to 181 subjects, including 26 normal subjects, 14 patients with arterial hypertension, 35 patients with gastrointestinal disease, and 106 patients with atherosclerosis (41 combined with arterial hypertension, and 27 combined with gastrointestinal disease). There were no sig-

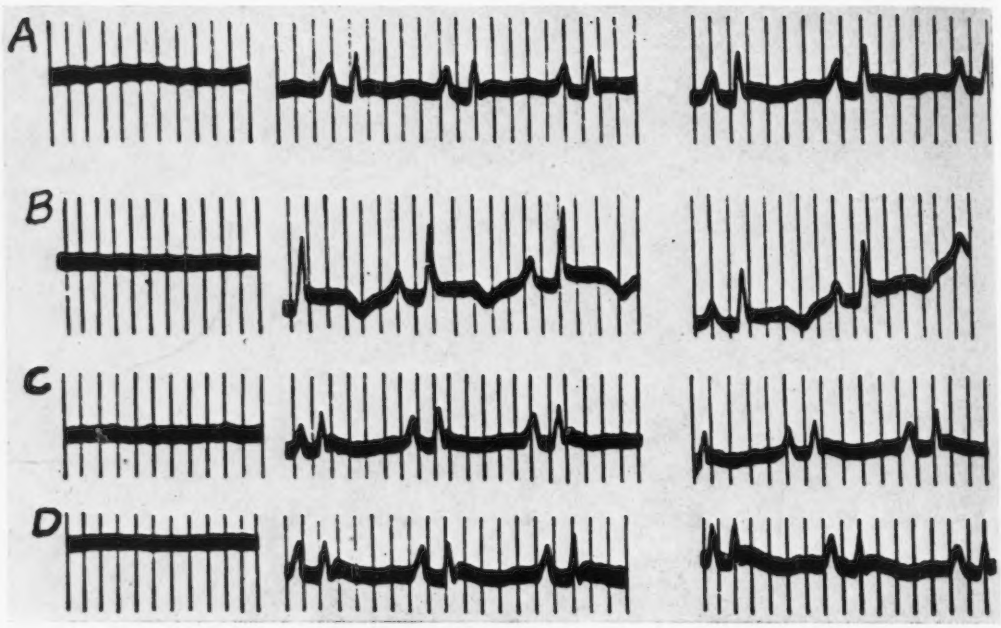

Figure 2

Electrocardiogram of a cat with experimental myocarditis. Leads I-III. A, *before perfusion of isolated loop;* B, *injection of 20 gamma acetylcholine;* C, *10 minutes later;* D, *injection of acetycholine after preceding injection of procaine. (Reproduced from Ganelina,[19] figure 2).*

nificant electrocardiographic changes in 57 placebo experiments (empty starch capsules).[23]

"Large" changes of the electrocardiogram (as defined by the author) occurred 15 to 25 minutes after ingestion of the mustard capsule in 51 of the 106 patients with atherosclerosis, in 12 of 35 patients with gastrointestinal disease, in 4 of 14 hypertensive patients, and in 3 of the 26 control subjects. In patients with coronary heart disease, the changes occurred in the S-T segment and T wave, whereas in patients with gastrointestinal disease prolongation of the P-R interval (with or without changes of T) was more frequent. The "large" changes were less frequent in advanced coronary disease than in an earlier phase, possibly due to greater rigidity of coronary vessels. In about half of the patients with larger electrocardiographic changes after mustard ingestion, coronary artery disease was associated with gastrointestinal disorders, i.e., in 25 of the 27 patients in this group. The combination of gastrointestinal and coronary disease, therefore, increases greatly the frequency of electrocardiographic changes after mustard ingestion.

Ganelina also found a greater incidence of "large" electrocardiographic changes after mustard ingestion in patients with blood cholesterol over 200 per cent than in those below this value.[18] The scatter is fairly large, but according to Ganelina, the difference in the distribution approaches statistical significance. Ganelina considered the gastric stimulation with mustard as a comparatively mild stimulus, and expected greater electrocardiographic changes with increase of the stimulus strength. Since gastrointestinal disease (gastroenteritis, food poisoning) may involve strong chemical stimulation, Ganelina analyzed the records of 486 patients with myocardial infarction hospitalized from 1945 to 1952. In 15 patients, acute gastritis or gastroenteritis was considered to be present preceding myocardial infarction. Ganelina thought that acute gas-

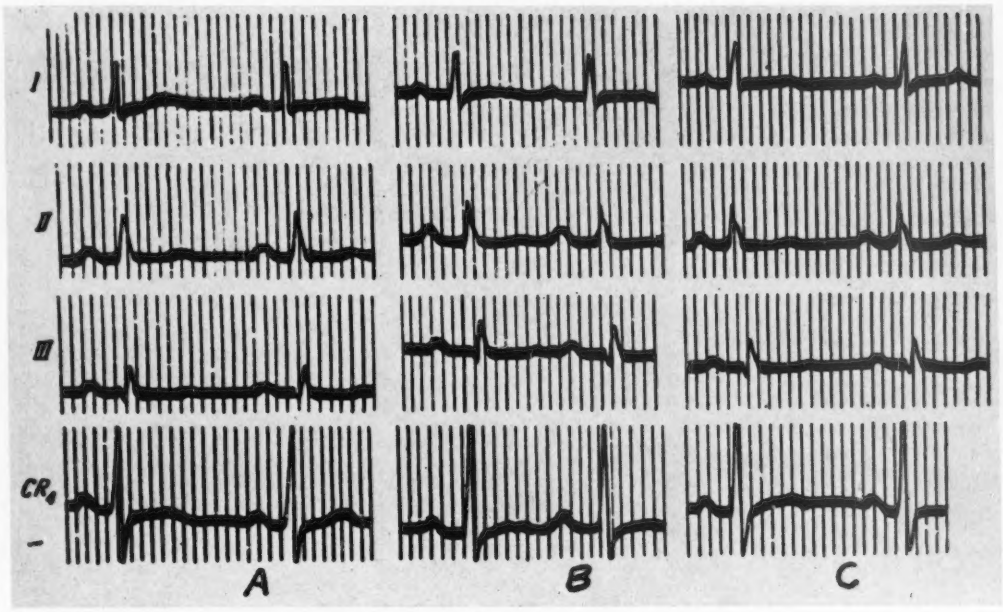

Figure 3

Electrocardiogram of a patient with coronary heart disease. A, *basal condition;* B, *after ingestion of a mustard capsule flattening of* T_1 *and* T_3, *slight notching of T in* CR_4, *prolongation of P-R interval;* C, *10 minutes later—reversal of changes. (Reproduced from Ganelina,*[19] *figure 1).*

troenteritis may be the direct underlying cause in the development of the infarct. This group of 15 patients is only a small percentage of the total, but apparently rigid criteria were used in the analysis of the charts, and the number of patients with gastroenteritis preceding the infarct may well have been larger. In acute myocardial infarction, gastrointestinal symptoms were present in the majority of patients,* and in one third of all cases there were data of previous gastrointestinal disease (gastritis, gastrointestinal infections, overeating, or large alcohol consumption). These results are corroborated by a case report of Prikazchikov and Petrova;[25] severe coronary insufficiency with T inversion in CR_4 to CR_6 developed in a patient with intestinal arterial occlusion. Ganelina, on the basis of her experiments and clinical data, considered the presence of gastrointestinal disease in patients with coronary heart disease as a major contributing factor in the development of acute coronary insufficiency and myocardial infarction, and not merely as a symptom of it. The results stress the importance of treatment of gastrointestinal disorders, and of a proper dietary regime, in coronary artery disease.

Since meal intake includes mechanical as well as chemical gastrointestinal stimulation, the reflex mechanisms investigated by Ganelina may well be involved in the electrocardiographic changes after meals,[26] and particularly in the abnormal response in a substantial percentage of patients with coronary artery disease.[24] As a diagnostic test the meal test appears to be superior to Ganelina's mustard test, because of the availability of a larger, statistically analyzed control group[26] and the more pronounced electrocardiographic changes in a positive meal test.[24] Ganelina, however, was primarily concerned

*The number of patients and the time of observation and not given, but probably refer to more recent material, and the prevalence of gastrointestinal symptoms in myocardial infarction corresponds to general experience.

with the mechanism involved and its significance in coronary insufficiency and myocardial infarction.

It seems that the possibility of reflex gastrointestinal symptoms in acute myocardial infarction should also be considered, or in other words, a two-way reflex situation resulting in a vicious circle. Even if the gastrointestinal symptoms are secondary, they may well be a complicating factor in the extent or severity of the infarction or ventricular ischemia, according to Ganelina's results.

Summario in Interlingua

Ab le vaste litteratura russe relative al thema sub discussion, illustrative datos clinic e experimental es citate in supporto del these de un effecto de reflexos ab receptores gastrointestinal super insufficientia coronari.

In conclusion le autor nota le possibilitate del phenomeno contrari, i.e. de symptomas gastrointestinal como reflexo de acute infarcimento myocardial.

References

1. Simonson, E.: Editorial: Cardiovascular research in Russia. Circulation **19**: 481, 1959.
2. —, and Brozek, J.: Russian research on arterial hypertension. Ann. Int. Med. **50**: 129, 1959.
3. Chernogorov, I. A.: Angina pectoris, Grudnaia Zhaba. Medgiz, Moscow, 1954, 159 pp.
4. Speranskii, N. T., and Ostroskaia, V. I.: Role of nervous factors in angina pectoris. Sov. Medits. **19**: 41, 1955.
5. Magakiaiv, G. O., Miminoshvili, D. I., and Kokaia, N. G. I.: Experimental investigation of the pathogenesis of hypertension and coronary insufficiency. Klinich. Med. **37**: 30, 1956.
6. Vovsi, M. S.: Clinic and pathogenesis of acute coronary insufficiency (angina pectoris). Terap. Arkh. **29**: 19, 1957.
7. Zamislova, K. N., and Bodnar, L. P.: State of the central nervous system in coronary insufficiency, Aterosklerosis i Koronarnaia Nedostatochnost'. Moscow, Medgiz, 1956, 249 pp.
8. Gukasyan, A. G., and Tapitser, E. I.: Etiological and clinical problems in myocardial infarction. Terap. Arkh. **24**: 13, 1952.
9. Lebedinskii, A. V., Medvedev, V. I., and Peimer, I. A.: Importance of coronary spasm in the pathogenesis of coronary insufficiency. Tesicy zaced. biuro otdel. Med.-Biol./Nauk. Nauk Akad. Med. SSSR, Sukhumi, 1954, p. 32.
10. Smirnov, A. I.: On experimental myocardial infarction. Tesisy zased. biuro Med.-Biol. Nauk, AMN, SSSR, Sirkhumi, 1954, p. 50.
11. Kuzmina-Prigradova, A. V.: Collateral circulation after ligation of the anterior descending coronary artery, and effect of vagal stimulation. Experiments on dogs. Bull. eksp. biol. i. med. **42**: 67, 1956.
12. Lapin, V. A.: Pathogenesis of myocardial infarction. Bull. eksp. biol. i. med. **40**: 19, 1955.
13. Yushchenko, N. A.: Experimental coronary insufficiency. Dokl. Akad. Nauk. **112**: 782, 1957.
14. Ostapiuk, F. E.: Intrathoracic novocaine anesthesia in coronary insufficiency. Terap. Arkh. **29**: 58, 1957.
15. Bulatov, P. K., and Stukkei, M. A.: Therapy of patients with chronic coronary insufficiency by means of novocaine block of the anterior mediastinum. Klinich. Med. **38**: 42, 1960.
16. von Bergman, G.: Das "Epinephrale Syndrom," seine Beziehung zur Angina Pectoris und zum Kardiospamus. Deutsche med. Wchnschr. **58**: 605, 1932.
17. Gilbert, N. C., Fenn, G. K., and LeRoy, G. V.: The effect of distention of abdominal viscera on the coronary blood flow and on angina pectoris. J.A.M.A. **115**: 1962, 1940.
18. Ganelina, I. E.: Reflexes from the pressor receptors of the intestinal tract and urinary bladder on the heart in experimental neurogenic hypertension and atherosclerosis. Bull. eksp. biol. i. med. **20**: 35, 1955.
19. —: The role of visceral reflexes in clinic and pathogenesis of atherosclerosis. Trudy Bsjecoyuz. c'esda terap. **14**: 66, 1956.
20. —: Reflexes from intestinal chemoreceptors on the heart in experimental myocarditis. Bull. eksp. biol. i. med. **22**: 31, 1957.
21. —: Further studies on reflexes from the chemoreceptros of the intestinal tract on the heart. Trudy Inst. Fiziol. (T. P. Pavlov) **7**: 310, 1958.
22. —: Reflexes from gastro-intestinal chemoreflexes. Electrocardiographic data, Trudy Inst. Klin. i. eksper. Kardiol. ANGSSR. **5**: 285, 1958.
23. —: Reflexes from the chemoreceptors of the intestinal tract on the heart particularly in atherosclerosis, Diss. 1st Lening. Med. Inst., Leningrad, 1957, 33 pp.
24. Simonson, E., and McKinlay, C. A.: The meal test in clinical electrocardiography. Circulation **1**: 1006, 1950.
25. Prikazchikov, A. T., and Petrova, V. M.: On reflex myocardial infarction, Klinich. Med. **32**: 62, 1954.
26. Simonson, E., and Keys, A.: The effect of an ordinary meal on the electrocardiogram. Normal standards in middle-aged men and women. Circulation **1**: 1000, 1950.

ABSTRACTS

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Abstracters

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PHYSICAL SIGNS

Vogelpoel, L., Nellen, M., Swanepoel, A., and Schrire, V.: The Use of Amyl Nitrite in the Diagnosis of Systolic Murmurs. Lancet 2: 810 (Nov. 14), 1959.

Inhalation of amyl nitrite produces an initial drop in systemic blood pressure followed by increased filling of the right heart and increased forward flow. The authors describe its effect on systolic murmurs of various causes and its use in diagnosis. Murmurs were carefully noted and amyl nitrite was then inhaled. Marked tachycardia and flush signaled the end point. Hypotension and tachycardia persisted for 20 to 30 seconds. The aortic second sound always became softer because of hypotension and the first sound much louder because of tachycardia. A summation gallop frequently developed. Left-sided regurgitant systolic murmurs became shorter and softer, the change being maximal shortly after inhalation. In small ventricular septal defects, the softening and shortening of the murmur were shown to be due to the pronounced drop in pressure gradient between left and right ventricle. In large ventricular septal defects, the effect was less consistent. In patent ductus, a marked reduction of the aorticopulmonary gradient accounted for the disappearance of the diastolic component and marked shortening of the systolic murmur. In mitral incompetence, the left ventricular-left atrial gradient was reduced, and the murmur was shortened but the murmur of tricuspid incompetence was increased. With the exception of Fallot's tetralogy, ejection murmurs became louder. The increase in loudness was much greater and more sustained when the murmur resulted from organic stenosis than from increased flow. It was more striking in pulmonary than in aortic stenosis. In ejection murmurs not due to stenosis, the increased loudness was seldom great and simply paralleled the increased cardiac rate. The presence of combined lesions modified the response according to the relative size of the defects. Changes in diastolic murmurs also occurred consistent with the above hemodynamic changes. The effect of amyl nitrite was much less striking when cardiac failure was present or imminent. This test, which is simple and harmless, can be of help in the bedside differentiation of ventricular septal defect from pulmonary stenosis, pulmonary stenosis from Fallot's tetralogy, and aortic stenosis from mitral incompetence.

KURLAND

PHYSIOLOGY

Abel, H.: On the Relation of the Ventricular Gradient to Stroke Volume. Ztschr. Kreislaufforsch. 48: 757 (Aug.), 1959.

In 12 normal persons or patients with mild hypertension exercise caused increase of ventricular stroke volume (determined from the force-free displacement ballistocardiogram of Klensch) accompanied by diminished amplitude of the frontal plane ventricular gradient (QRST area). However, the heart rate was always accelerated. Changes of the intrapulmonary pressure caused the stroke volume in some cases to decrease about 3 times without change of heart rate or ventricular gradient. In some cases, increase of stroke volume was accompanied by a decrease of the gradient, but this was caused by decreased area of the QRS complex while the T wave showed no significant changes. It is concluded that physio-

logic changes of ventricular stroke volume alone do not cause any significant changes of the ventricular gradient.

LEPESCHKIN

Benitez, D., Holmgren, B., and Middleton, S.: Sympathetic Cardiac Stimulating Fibers in the Vagi. Am. J. Physiol. 197: 739 (Oct.), 1959.

The cardiac effects obtained by stimulation of the vagus nerve were studied in the isolated heart preparation of cats, perfused with Tyrode's solution according to Langendorff's technic. High cervical stimulation of the vagus produced slight or no positive inotropic and chronotropic effects in the atropinized heart. Excitation of the thoracic portion produced intense cardiac stimulation. The cardiac stimulating effect was not influenced by supra-nodose or infra-nodose vagotomy. Complete cervical and upper thoracic sympathectomy abolished vagal cardiac stimulation. It is concluded that sympathetic fibers that join the vagal trunk at the lower cervical and, perhaps, the upper thoracic level, are responsible for the positive chronotropic and inotropic effects obtained when stimulating the intact or degenerated vagus nerve.

KAYDEN

Cooper, T., Willman, V. L., Zafiracopoulos, P., and Hanlon, C. R.: Effect of Prophylactic Digitalization on Myocardial Function after Elective Cardiac Arrest. Ann. Surg. 151: 17 (Jan.), 1960.

It has been observed that myocardial failure is a principal cause of mortality and morbidity after extended periods of elective cardiac arrest. It is also known that digitalis improves cardiac function in the presence of cardiac failure. This study was undertaken to determine what predigitalization would accomplish in improving the cardiac function of cardiac arrest induced by potassium citrate in the normothermic dog. Cardiac output, mean arterial pressure, and left ventricular stroke work were calculated before and after cardiac arrest. Cardiac output and left ventricular stroke work were markedly reduced following arrest. Blood pressure was maintained due to evident increased peripheral vasoconstriction. In all 6 animals given predigitalization, cardiac output, although depressed, was significantly better than in the control animals. Left ventricular stroke work was 20 grammeters compared with the nondigitalized group, which were unable to exceed 9.1 grammeters. Similar results have been reported by these investigators when hypothermia was employed instead of predigitalization. The mechanism by which this occurs is unknown. Whether on this basis predigitalization is warranted in the nonfailing heart is questioned because of the possibility of induced serious arrhythmias and the tendency of digitalis to reduce cardiac output. However, this study does provide evidence favoring predigitalization as a possible means for reducing morbidity and mortality when cardioplegia must be used.

LEVINSON

Cope, R. L.: Suppressive Effect of Carotid Sinus Stimulation on Premature Ventricular Beats in Certain Instances. Am. J. Cardiol. 4: 314 (Sept.), 1959.

Stimulation of one or the other carotid sinus repeatedly was found to abolish or decrease the number of premature ventricular beats in 8 patients aged 30 to 78 years, only 1 of whom had evident organic heart disease. The effect began promptly after onset of stimulation and continued for varying periods afterward. The heart rates were usually rapid before stimulation and slowing regularly occurred. The possible mechanisms of premature ventricular beat suppression are discussed, particularly those related to nervous influences.

ROGERS

Daly, I. de B., and Daly, M. de B.: The Effects of Stimulation of the Carotid Body Chemoreceptors on the Pulmonary Vascular Bed in the Dog: The "Vasosensory Controlled Perfused Living Animal" Preparation. J. Physiol. 148: 201 (Oct.), 1959.

A dog preparation is described in which blood flow through the greater and lesser circulations is under independent control and in which separate perfusions of the carotid bifurcation, aortic arch, cerebral regions and vascular bed of the abdominal aorta are maintained. By this technic, it is possible to determine the reflex response in any vascular territory uncomplicated by the effects of secondary reflex or humoral stimuli produced by the primary stimulus. Stimulation of the carotid body chemoreceptors with hypoxic blood produced unpredictable changes in the pulmonary vascular resistance when blood was flowing through the bronchial vascular system but if the bronchial blood flow was temporarily interrupted, the chemoreceptor stimulation invariably produced an increase in pulmonary vascular resistance. The authors concluded that carotid chemoreceptor stimulation produced pulmonary vascular constriction but this response could be masked by a passive mechanism such as the hemodynamic effects of blood flowing through the bronchial circulation.

KARPMAN

Daly, I. de B., and Daly, M. de B.: The Effects of Stimulation of the Carotid Sinus Baroreceptors on the Pulmonary Vascular Bed in the Dog. J. Physiol. **148**: 220 (Oct.), 1959.

The carotid sinus baroreceptors were stimulated by raising the carotid sinus pressure in dog preparations in which the pulmonary circulation and areas of the systemic circulation (i.e., the carotid bifurcations and aortic arch, the brain, the remainder of the systemic circulation) were individually perfused. Carotid sinus distention produced a reduction of pulmonary vascular resistance when blood was flowing through the bronchial vascular system and also when the bronchial circulation was temporarily interrupted. The authors concluded that reduction of the pulmonary vascular resistance was caused by a primary reflex dilatation of the pulmonary vascular bed due to the inhibition of sympathetic vasoconstrictor tone.

KARPMAN

Dawes, G. S.: Some Respiratory and Cardiovascular Problems after Birth. Arch. Dis. Child. **34**: 281 (Aug.), 1959.

The author extensively reviewed animal experiments that were of importance in the areas of stillbirth, immaturity, atelectasis, postnasal asphyxia, and spastic paralysis. Emphasis was placed on the fact that for some days after birth, the anatomic pathways, which are usually thought of as peculiar to the fetus, (i.e., patent ductus arteriosus, foramen ovale) are still not firmly shut; one must therefore be alerted to possible left-to-right or even right-to-left (i.e., as occurs with asphyxia) shunts in the newborn. Within a day after birth, oxygen consumption increases 3-fold but it falls off in the anoxic newborn animal. Evidence exists which supports the concept that there is a full range of respiratory reflexes at birth at the neutral temperature and that oxygen consumption increases if the environmental temperature is lowered. The author also points out experiments which indicate that almost every baby at birth has had its carbohydrate reserves depleted by glycolysis and begins life with a low blood pH (which may explain why some infants breathe so poorly at birth). The conclusions are that the newborn animal is not a helpless and weak, miniature adult but rather is a complicated, highly integrated organism that deserves study for its own sake.

KARPMAN

Hughes, H. E., and Magovern, G. J.: The Relationship between Right Atrial Pressure and Blood Volume. Arch. Surg. **79**: 238 (Aug.), 1959.

A method of localization of an intracardiac catheter is presented utilizing an intracardiac electrode. Standard methods of determining blood volume were correlated with continuous monitoring of right atrial pressure in 25 patients after thoracotomy. This monitor was a sensitive reflection of changes in the cardiovascular system. It accurately and instantaneously reflected the pressure of the venous return as it entered the right heart, i.e., it determined whether the compensatory mechanisms, which were brought into existence to restore and maintain hemodynamic equilibrium and maintain normal cardiac output, were adequate. If there were hypovolemia, the fall in central venous pressure would reflect a decrease in venous return and thus a loss of effective circulating blood volume. If adequate blood replacement was then given, this was reversed. However, if there was intrinsic myocardial damage, arrhythmia, or overloading of the vascular tree, the central venous pressure would remain normal or high even though there was tachycardia and peripheral hypotension. Further overloading of the vascular tree and compromise of the heart would be avoided. Although an actual decrease in blood volume may be present, if the venous pressure is normal, the amount of blood present is all the heart can handle at that time. Thus, the continuous monitoring of the central venous pressure will reflect the effective circulating blood volume at any particular time. The peripheral venous pressure is not as good an index because the peripheral veins are subjected to extramural pressures and because there is some element of constriction of venous channels at their point of entrance into the thoracic cavity. It is suggested that this method be adopted for any patient in whom suspected alteration of hemodynamics may be of significant importance.

SHEPS

Jones, W. B., Hefner, L. L., Bancroft, W. H. Jr., and Klip, W.: Velocity of Blood Flow and Stroke Volume Obtained from the Pressure Pulse. J. Clin. Invest. **38**: 2087 (Nov.), 1959.

The method described by the authors determines continuous blood velocity in the aorta of dogs by a single-lumen catheter. The system is based on the Navier-Stokes equation and uses an electronic computer to solve the equation. From the area under the velocity curve the cardiac output was determined. This was compared with the cardiac output determined simultaneously with the dye-dilution technic. A correlation coefficient of 0.97 was obtained.

KAYDEN

König, K., Reindell, H., Steim, H., and Musshoff, K.: Contribution to the Hemodynamics of Hypertensive Regulatory Disturbances. Ztschr. Kreislaufforsch. 48: 923 (Oct.) 1959.

In 9 trained and 13 untrained normal persons as well as in 5 persons with hypertension the oxygen consumption was determined with the closed-system method, and blood samples were taken from the brachial and pulmonary arteries, at rest and during exercise on the bicycle ergometer. In 4 patients with hypertension the cardiac output (Fick's method) was considerably elevated at rest and during exercise of all intensities; in 2 of these the elevation was caused by an elevated stroke volume while in the other 2 it was caused by an elevated heart rate. The arteriovenous oxygen gradient was considerably decreased in all these cases. In 1 patient with hypertension the latter was caused by elevation of peripheral resistance at rest and during exercise, since the heart output was normal, the stroke volume very small, and the heart rate very high. An additional patient with a norepinephrine-secreting pheochromocytoma showed a similar behavior. Oxygen consumption during exercise was normal in all patients. The oxygen pulse (oxygen consumption divided by the heart rate) proved a usable criterion of the stroke volume in submaximal exercise. Based on these results, the conclusion is reached that hypertension caused by increased peripheral resistance corresponds to a small heart while that caused by increased heart output corresponds to a large heart.

LEPESCHKIN

Maxwell, G. M., Castillo, C. A., Clifford, J. E., Crumpton, C. W., and Rowe, G. G.: Effect of Serotonin (5-Hydroxytryptamine), on the Systemic and Coronary Vascular Bed of the Dog. Am. J. Physiol. 197: 736 (Oct.), 1959.

Dogs were anesthetized with morphine and Dial-urethan-Nembutal. Cardiac output (Fick) and coronary blood flow (N_2O Fick) were measured before and after the mechanical infusion of 20 μg./Kg./minute of serotonin over a period of 25 minutes. The results showed an increase in heart rate, pulmonary arterial pressure, and right ventricular work. Systemic blood pressure and resistance were reduced. Coronary blood flow increased by 79 per cent, with an increase of coronary sinus oxygen content of 3.3 volumes per cent. Cardiac oxygen consumption and carbon dioxide production increased. Mechanical efficiency of the left ventricle fell by 3 per cent. Serotonin appears to act as a powerful coronary vasodilator, increasing the oxygen supply to the myocardium without increasing left ventricular work.

KAYDEN

Melville, K. I., and Shister, H. E.: Cardiac Responses to Epinephrine and Norepinephrine during Prolonged Cholesterol and High Fat Feeding in Rabbits. Am. J. Cardiol. 4: 391 (Sept.), 1959.

Rabbits consuming a chow with supplements of 2 per cent cholesterol and 6 per cent corn oil developed gross coronary atherosclerosis and elevated serum cholesterol levels in periods of 4 to 12 weeks. However, continuation of the fat feeding for 38 weeks was attended by no significant electrocardiographic S-T segment or T-wave changes. The intravenous injection of 0.1 to 0.5 mg. of epinephrine was followed by marked ventricular arrhythmias and even fatal fibrillation in both normal and fat-fed animals, although S-T segment and T-wave changes were not seen. The injection of 0.1 to 0.2 mg. of norepinephrine was followed by paroxysmal atrial tachycardia only in the fat-fed animals, but with higher doses tachycardias also developed in normal rabbits. Most of these rabbits developed S-T segment and T-wave depression, but ventricular fibrillation was not observed. A less-than-normal increase of coronary blood flow and of myocardial contractility resulted from administration of either amine to the atherosclerotic excised heart. It was concluded that norepinephrine is less injurious than epinephrine to both the normal and the atherosclerotic heart.

ROGERS

Musshoff, K., Reindell, H., and Klepzig, H.: Stroke Volume, Arteriovenous Difference, Cardiac Output and Physical Working Capacity and Their Relationship to Heart Volume. Acta cardiol. 14: 427, 1959.

Heart volume, stroke volume, cardiac output, and arteriovenous difference were measured in healthy persons (13 men, 4 women, and 9 highly trained male athletes). At rest, there was no significant correlation between heart volume, stroke volume, cardiac output, and arteriovenous difference. During graded, progressively raised levels of exercise in the "steady rate," stroke volume, cardiac output, and arteriovenous differences increased significantly. Contrary to the findings at rest, there was a statistically significant correlation between heart volume, on the one hand, and maximal values of stroke volume, cardiac output, and oxygen-pulse (oxygen consumption per heart beat), on the other. The working capacity and efficiency of the circulation, and its ability to increase stroke volume and cardiac output during exercise were greater the larger the heart volume. At the same level of exercise, the peripheral oxygen uptake was identical in all 3 groups (men, women, athletes); i.e., the arterio-

venous difference was directly related to work. Since the largest hearts were able to perform the most work, associated with the highest arteriovenous difference, there was also a positive correlation between heart volume and maximal arteriovenous difference. These findings were considered incompatible with an unmodified application to the healthy heart of the Law of the Heart, as propounded by Frank, Starling, and Straub.

BRACHFELD

Richardson, D. J., Gahagan, L. H., Lewis, W. H., Jr., Sheehan, D., DeBeer, E. J., Calville, K. I., and Ellis, C. H.: Cardiovascular Responses to Transcranial Electric Stimulation in Man and Dog. J.A.M.A. **171:** 528 (Oct. 3), 1959.

Transcranial electric stimulation, as used in electroconvulsive therapy, is a stressor profoundly affecting the cardiovascular system. Cardiovascular responses to this appear to be identical in man and in the dog. Therefore, animal and human studies have been used in attempting to elucidate the underlying mechanisms. Four hundred treatments were studied in man. Most of these patients received thiopental intravenously before treatment; all received succinyl-choline chloride and artificial ventilation with oxygen during the period of apnea. Vagal arrhythmias did not occur in patients who had received atropine, but occurred frequently in patients who had not. Extravagal arrhythmias occurred frequently and were not uniformly preventable by either chlorpromazine or quinidine therapy. All patients had transitory increases in systolic blood pressure. These increases were half as great in patients who had received tetraethylammonium chloride as in patients who were not so protected. Experiments involving bilateral adrenalectomy and transection of the spinal cord in dogs corroborated the impression that both vagal and extravagal mechanisms are activated by electroconvulsive treatment and can be depressed by appropriate medications.

KITCHELL

Schütz, E., and Schmitt, G.: Recovery of Cardiac Muscle after Strain Caused by Paroxysmal Tachycardia. Ztschr. Kreislaufforsch. **48:** 708 (Aug.), 1959.

The duration of the action potential of frog ventricular muscle strips suspended in air increases with the interval between stimulation and the end of the preceding action potential; this duration gradually approaches a constant value when the interval exceeds 4 to 7 seconds. When the muscle strips were stimulated following an artificially produced paroxysmal tachycardia (at rates of 36 to 96 per minute), lasting 4 to 10 seconds, the curve expressing the duration of the action potential as a function of the stimulus interval from the end of the preceding action potential did not approach a constant value until after 8 to 26 seconds, and showed an irregular rather than a smooth course. The irregularities appeared usually at 1 to 3 seconds and again at 8 to 13 seconds. A similar course of the curve was found if the strips were placed for 12 to 23 minutes into a hypotonic (0.3-9.4 per cent) sodium chloride solution or for 5 minutes into a 2,4-dinitrophenol solution. These effects, as well as those of tachycardia of long duration, are attributed to changes in the myocardial cell membrane. When the muscle was stimulated during the descending branch of the previous action potential, the response appeared after a delay up to 0.2 second, or it was followed by a short nonconducted action potential and then by a regular action potential with a very slow ascent.

LEPESCHKIN

Smith, D. J., Parker, R. C., Hanna, C., and Curley, H. E.: Subacute and Late Cardiovascular Sequelae to Low Doses of Gamma Radiation. Am. J. Physiol. **197:** 725 (Oct.), 1959.

A battery of in vivo and in vitro tests of cardiovascular performance was used to assess the effects of whole-body gamma radiation (cobalt 60) upon the cardiovascular system of dogs. A new method for study of the pressure-volume relations of isolated surviving arteries is described. Groups of 6 beagles were exposed to 30r and 100r 22 months before death and compared with littermate controls. No differences between irradiated and control dogs could be demonstrated. Eight mongrel dogs received 300r 30 days before death and were compared with 5 mongrel controls. The only significant difference observed was in the pressure-volume curves of arteries from irradiated dogs, these vessels having a greater initial tone than control arteries. It was concluded that 30r and 100r of whole-body gamma radiation had no demonstrable effects upon the cardiovascular system of dogs irradiated 22 months before study, but that 300r of gamma radiation did produce a significant abnormality of blood vessels.

KAYDEN

Stubbs, J., and Widdas, W. F.: The Interrelationship of Weight Change and Coronary Flow in the Isolated Perfused Rabbit Heart. J. Physiol. **148:** 403 (Oct.), 1959.

The isolated perfused rabbit heart was used to study the interrelationship of cardiac weight change and coronary flow. Epinephrine, ionized calcium, extrasystoles, Pitressin, hypertonic solu-

tions, and cessation of perfusion all caused temporary weight loss with different but predictable effects on the coronary flow; acetylcholine and potassium citrate produced weight gain associated with increased coronary flow. The authors concluded that the variations of coronary flow in the isolated heart depend, in part, on the physical support given by the myocardium and the interstitial fluid. In vivo, the coronary circulation is apparently influenced by the integration of many factors, some acting on the vasculature per se, whereas others act upon extravascular phenomena such as the strength and duration of the systolic contraction of the myocardium.

KARPMAN

Van Den Heuvel-Heymans, G. M., and Rovati, A. L.: Carotid Sinus Baroreceptors and Pulmonary Haemodynamics. Arch. int. pharmacodyn. **121**: 169, 1959.

The effects of carotid sinus baroreceptor reflexes on the pulmonary hemodynamics was investigated in the anesthetized dog. Occlusion of the common carotid arteries (decrease of baroreceptor stimulation) caused mostly a rise in systemic arterial pressure and in pulmonary arterial and venous pressures. The pulmonary arterial and venous pressures were unaffected by occlusion of the common carotid arteries, if the systemic arterial pressure was not increased or only slightly so. Previous section of the vagi-aortic nerves increased the responses in both systemic and pulmonary pressures after occlusion of the common carotid arteries. Local carotid sinus application of norepinephrine in vagotomized dogs provoked a reflex fall of the systemic arterial pressure, while the pulmonary arterial pressure remained unchanged until low levels in the systemic arterial pressure had been reached. From these low levels on, the pulmonary arterial pressure also decreased. Section of the vagi-aortic nerves in normal dogs mostly induced tachycardia and increases in both systemic and pulmonary arterial pressures, while the pulmonary venous pressure decreased in most cases and increased in some cases.

BRACHFELD

Weissler, A. M., Leonard, J. J., and Warren, J. V.: The Hemodynamic Effects of Isoproterenol in Man. J. Lab. & Clin. Med. **53**: 921 (June), 1959.

An experiment on 12 normal male university students is described as further support to the thesis that the central venous pool acts as an important factor limiting increases in cardiac output and stroke volume. Six subjects were studied in the recumbent posture and 6 in the passive 60-degree, head-up, tilt position during intravenous infusion of isoproterenol (Isuprel). Significant elevations in cardiac output and stroke volume, associated with slight increases in pulse rate, occurred in the supine subjects. Average pulse rate increases were the same in the tilted subjects as in the recumbent ones, but minute and stroke volume responses were considerably less in the former. Depletion of thoracic reservoirs of blood in the upright posture appeared to limit cardiac output and stroke volume responsiveness. The effect was even greater with atropine, which acts primarily on the heart rate, rather than on myocardial contractility.

MAXWELL

Wolfe, K. B.: Damage to the Brain Following Anoxia in Dogs: Observations Following Asphyxia, Cardiac Arrest and Ventricular Fibrillation. Am. J. Cardiol. **4**: 229 (Aug.), 1959.

Seventy-seven normal anesthetized dogs tolerated electrically induced ventricular fibrillation for 2 minutes without evident cerebral damage. Fifty dogs were asphyxiated by clamping their endotracheal tube. The wink reflex disappeared on an average of 3½ minutes later, and the aortic pulse stopped in 5½ minutes. Asphyxia was maintained 2 minutes longer, the total period ranging from 4½ to 9½ minutes. By this time the heart had gradually weakened, dilated, and stopped, but did not fibrillate. Then the lungs were oxygenated and the heart beat was restored by hand. Seventeen per cent developed easily reversible ventricular fibrillation as the heart was reoxygenated. Twenty-four hours later, 14 dogs had died from cerebral damage, 18 survived with severe brain damage and 18 showed slight or moderate neurologic disturbance.

ROGERS

PULMONARY DISEASES

Jose, A. D., and Milnor, W. R.: The Demonstration of Pulmonary Arteriovenous Shunts in Normal Human Subjects, and Their Increase in Certain Disease States. J. Clin. Invest. **38**: 1915 (Nov.), 1959.

The recording of arterial saturation changes by a cuvette densitometer during the Valsalva maneuver provided a direct and continuous record of arterial oxygen saturation. In the absence of intracardiac shunts, a consistent pattern of change in saturation was found, consisting in a rise in saturation during the maneuver and a fall in saturation following cessation of the maneuver. In 9 normal subjects the saturation rise averaged 1.2 per cent, while in 6 patients without cardiac or pulmonary disease, saturation rises of from

3.9 to 7.3 per cent occurred during the maneuver. It is suggested that the saturation rise results from a decrease in blood flow through pulmonary arteriovenous shunts, and that those patients with a large rise in saturation had abnormally large flow through the shunts at rest. The transmural pulmonary artery pressure may well be an important factor in controlling flow through these shunts, and an abnormally large shunt flow may occur in patients with chronic pulmonary hypertension. In normal subjects the shunt flow at rest measured approximately 1 per cent of total pulmonary flow. In 14 patients with cardiac or pulmonary disease but without intracardiac shunts or signs of congestive heart failure, each patient showed evidence of shunt flow at rest. It was abnormally large in 6 of the 14 patients, amounting to 20 per cent of total pulmonary flow in 1 subject. Two patients with congestive heart failure showed no changes in arterial saturation during or after the Valsalva maneuver.

KAYDEN

Kellaway, G.: Acute Anoxic Cardiac Failure in Pulmonary Heart-Disease. Lancet 2: 768 (Nov. 7), 1959.

Three hundred and thirty-four consecutive patients admitted to an Edinburgh hospital with congestive cardiac failure were reviewed. In 25 per cent there was a history of chronic lung disease and in 15 per cent this was the sole etiologic factor. Of the latter, 44 were in acute cardiac failure. The mortality rate was 41 per cent. Of all factors studied, only the electrocardiogram bore a relationship to the prognosis; three fourths of those with right ventricular strain failed to survive. A program of therapy was tried on all patients admitted with acute cardiac failure caused by pulmonary heart disease with right ventricular hypertrophy on the electrocardiogram. The principle of treatment was to provide continuous oxygen therapy, avoiding carbon dioxide narcosis by the frequent use of respiratory stimulants, nikethamide, and aminophenazole. Eighteen patients were treated; in no instance did carbon dioxide narcosis necessitate discontinuance of oxygen therapy. Five of the 18 patients died, a reduction in mortality rate from 74 to 28 per cent. Only 1 died as the direct result of pulmonary heart disease. Satisfactory oxygenation and clinical improvement were evident within 3 days. Edema tended to increase and required an average of 15 days for disappearance. Oliguria persisted for days after arterial oxygen saturation had been raised to normal.

KURLAND

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Brodsky, W. A., and Satran, R.: Comparison of Effects of Acidosis and Alkalosis on the Renal Action of Diamox. Am. J. Physiol. 197: 585 (Sept.), 1959.

Diamox was given to anesthetized hydropenic dogs by single intravenous injection in doses of 10 to 1,000 mg./Kg. to establish a dose-response pattern. Increments of urine bicarbonate excretion were 60 μM/minute after doses of 10 mg./Kg., 400 to 500 μM/minute after doses of 100 mg./Kg., 700 to 1,000 μM/minute after doses of 300 mg./Kg., and 600 to 1,180 μM/minute after doses of 500 to 1,000 mg./Kg. Urine flow was dependent predominantly on effective osmotic load, indicating that the diuretic action of Diamox did not affect the distal mechanism for water transport. Bicarbonate accounted for 30 per cent of the urinary solutes. Alkalinizing effects of Diamox, similar to those of sodium bicarbonate, were found in doses over 300 mg./Kg. Hence, the dose used for evaluation of drug effect was restricted to the range of 20 to 200 mg./Kg. The action of Diamox was reduced to one half to one sixth of that expected when given to dogs under conditions of both metabolic and respiratory acidosis. For example, the increment of bicarbonate excretion was no more than 200 μM/minute after doses of 20 to 200 mg./Kg. Such suppression of a drug action during acidosis was independent of glomerular clearance as well as of serum levels of bicarbonate and sodium ions. The action of Diamox under conditions of metabolic alkalosis or under normal conditions was greater than that observed under acidotic conditions. The relation of a postulated carrier-anhydrase molecule to Diamox inhibition under different conditions of plasma and urinary acidity is discussed.

KAYDEN

Klapproth, H. J., Takagi, H., and Corcoran, A. C.: Segmental Renal Ischemic Atrophy. Surgery 46: 1084 (Dec.), 1959.

Partial occlusion of segmental renal arterial branches was carried out in uninephrectomized dogs. The functional changes showed initial severe impairment of the affected segments with subsequent recovery attributable to adaption or hypertrophy of the untouched segments. The removal of the constriction did not relieve the hypertension and did not promote recovery of the atrophic segments from a morphologic or functional standpoint. Moreover renal function continued to deteriorate—probably due to persistent hypertension. In addition, hypertrophy of the unaffected segments was shown to obscure the effects of arterial branch lesions on the com-

position of the urine. These observations suggest that reconstruction of diseased branches of renal arteries may not be as effective in the relief of hypertension and renal changes as such procedures are in occlusive lesions of the main renal arteries. Excision of the atrophic segment would seem to be the procedure of choice in these situations. SHEPS

RHEUMATIC FEVER

Bernhard, G. C., and Stollerman, G. H.: Serum Inhibition of Streptococcal Diphosphopyridine Nucleotidase in Uncomplicated Streptococcal Pharyngitis and in Rheumatic Fever. J. Clin. Invest. 38: 1942 (Nov.), 1959.

An extracellular product of group A streptococci is diphosphopyridine nucleotidase. In human sera antistreptococcal diphosphopyridine nucleotidase activity (ASDA) can be measured as a specific antibody following streptococcal disease. In this report, the serum ASDA was studied in patients with rheumatic fever and in those with uncomplicated streptococcal pharyngitis. Serum ASDA is relatively heat stable and is associated with gamma globulins. It behaves in closely parallel fashion to other streptococcal antibodies in human sera. Increased ASDA was found approximately as frequently as increased antistreptolysin O and somewhat more frequently than increased antihyaluronidase or antistreptokinase titers. Mean ASDA titers were higher in the sera of patients with acute rheumatic fever than in the sera of uncomplicated streptococcal infection. After prolonged freedom from streptococcal infection, ASDA titers were uniformly low in patients with rheumatic fever. This response is entirely similar to other streptococcal antibodies in patients with rheumatic fever.

KAYDEN

De Silva, S.: Incidence of Rheumatic Fever in Ceylon. Arch. Dis. Child. 34: 247 (June), 1959.

Some form of rheumatic disease was diagnosed among 0.7 per cent of the 70,292 children admitted to the Children's Hospital in Colombo, Ceylon, during 1953-1957. The most common age of occurrence was in late childhood (from ages 9 to 12) and the disease appeared to run a rather mild course. Cardiac complications and over-all mortality were both less common than in the more temperate climates. Cutaneous signs and chorea were only rarely seen.

KARPMAN

Maynard, E. P., Jr., and Grover, V.: The Effect of Childbearing on the Course of Rheumatic Heart Disease: A 25-Year Study. Ann. Int. Med. 52: 163 (Jan.), 1960.

This study is of 455 women of the childbearing age group who had rheumatic heart disease. The authors have attempted to determine whether pregnancy affects the long-term prognosis in rheumatic heart disease. The records of a single clinic were used and the data were collected for a 25-year period. The authors indicate the statistical difficulties in analyzing this group for the effect of parity versus non parity on mortality. The selective effect of the very factor that is being studied creates a medical bias which precludes an unbiased answer to the question being studied. There are certain clinical impressions listed by the authors. No consistent differences between the parous and nonparous groups, were found with respect to age at first infection, number of episodes of infection prior to first observation, valvular lesion at first observation, or nature of the recorded infection. An important difference appeared to exist in the functional classification at first observation. The percentage in functional classification 1 was higher in the parous than in the nonparous group. It is suggested that women with poorer functional classification tend to be in the nonparous group, and this explains the higher mortality in nonparous women with rheumatic heart disease than in parous women with rheumatic heart disease.

KAYDEN

ROENTGENOLOGY

Arnois, D. C., Silverman, F. N., and Turner, M. E.: The Radiographic Evaluation of Pulmonary Vasculature in Children with Congenital Cardiovascular Disease. Radiology 72: 689 (May), 1959.

The increasing use of surgery in congenital malformations of the heart in children has required increasing diagnostic accuracy. The conventional chest film is the most common form of study in conjunction with clinical examination so it is important to use it as fully and accurately as possible. The status of the pulmonary vasculature is 1 criterion in interpreting these films. A test was made of the ability of radiologists to recognize pulmonary under- and over-vascularity by presenting the test readers with films of 32 patients agreed by another group of readers to demonstrate pulmonary over-vascularity. Another set of films of 32 patients who were agreed to demonstrate pulmonary under-vascularity was also used. The initial reading of these films was supported by special studies including cardiac catheterization, angiocardiography, operation, and in some instances necropsy. The 64 films were matched by age, sex, and radiologic technic

with normal chest films. The resultant 128 chest films were randomized and presented 3 times to each of 3 "readers." The first 2 readings were obtained with the chest obscured except for the lateral two thirds of the right hemithorax. The third reading was made with the entire chest film exposed as in a routine reading. There was no appreciable difference between readers or readings, but there was a distinct difference in the number of errors related to the recognition of pulmonary under- or over-vascularity. It is apparently much easier to recognize pulmonary over-vascularity than it is pulmonary under-vascularity in children with congenital malformations of the heart.

KITCHELL

Arnulf, G.: On Methodic Coronary Arteriography with the Aid of Acetylcholine. Arch. mal. coeur. **10:** 1140 (Oct.), 1959.

After extensive application of the method in dogs, 25 coronary arteriograms were completed without incident in patients, many with coronary disease. The procedure was best carried out in the supine position under general anesthesia with tracheal intubation. The smallest dose of acetylcholine necessary to cause ventricular standstill of 8 to 10 seconds was first determined in each patient; this is usually 0.1 to 0.2 Gm. This dose was dissolved in 10 ml. of physiologic serum and injected as rapidly as possible in the cubital vein. The standstill usually appeared 8 to 10 seconds after injection. A needle 14 cm. in length and 0.16 mm. in diameter was then introduced obliquely 2 cm. behind and lateral to the medial end of the clavicle, skirting the bone, toward the ascending aorta. Once the aorta had been penetrated, withdrawal of the mandrin caused red blood to spurt out. Under radiologic control, the needle was advanced until its point was within 1 to 2 cm. of the origin of the coronary arteries. A special syringe containing 50 ml. of 30 per cent "Vasurix 38," diluted with an equal volume of physiologic serum, was then attached to the syringe. Acetylcholine was then injected and as soon as cardiac standstill was demonstrated by the electrocardiogram, 10 ml. of the dye were injected and the first film was taken. Subsequent films were taken at 2-second intervals during the injection of the remaining dye. If standstill persisted for more than a few seconds after the last film, 1 mg. of atropine was injected into the aortic cannula; this caused immediate resumption of the heart beat. If cardiac standstill persisted during the procedure, the coronary arteries could be clearly demonstrated, allowing exact localization of the areas of stenosis or occlusion and direct evaluation of the effect of coronary dilating drugs or surgery.

LEPESCHKIN

Arnulf, G.: Systematic Coronary Arteriography with Acetylcholine Cardiac Arrest. Progr. Cardiovasc. Dis. **2:** 197 (Nov.), 1959.

Three hundred coronary arteriographic studies in dogs and 26 similar studies in patients with proved or suspected coronary artery disease were performed since 1956. In the human studies, acetylcholine was injected into a vein in the antecubital fossa or the hand. To obtain cardiac standstill of about 5 to 6 seconds, doses of 150 to 300 mg. of acetylcholine were used; the usual dose for a patient of 70 Kg. was 250 mg. The drug was diluted in 5 ml. of saline solution, injected rapidly, and "pushed" with 10 ml. of saline solution. The procedure was performed under general anesthesia to avoid the unpleasant effects of acetylcholine. The contrast agent used was Vasurix, a tri-iodide compound with 0.38 Gm. of iodine per ml. in a 75 per cent solution. The contrast agent was injected in the arch of the aorta with the use of a needle 15 cm. in length. The site of puncture was 2 cm. above and lateral to the inner extremity of the left clavicle. The standstill was of variable duration: 4 to 12 seconds. The only accident in the 26 patients studied was the injection of the contrast material outside the aorta into the mediastinum without any apparent untoward effects. Visualization of the coronary arteries was constant. The right coronary artery and the 2 branches of the left coronary artery were visualized in all patients. Coronary occlusions and collateral circulation were well seen.

KALMANSOHN

Bain, W. H.: Coronary Angiography. Scot. M. J. **4:** 527 (Nov.), 1959.

Coronary arteriograms of excellent technical quality have been produced in anesthetized dogs. Ventricular arrest was induced by injecting approximately 5 mg. of acetylcholine into the jugular vein. Then 10 ml. of 60 per cent Urografin were injected into the ascending aorta through a catheter or through a needle inserted via the suprasternal notch. One x-ray exposure was made immediately in 0.05 second, and optimum visualization was obtained in the left anterior oblique position. Injecting at the level of the aortic valve was avoided, since it often resulted in uneven filling of the 2 coronary arteries or in regurgitation of media into the left ventricle. In 200 ventricular arrests in dogs with and without ligation of the left anterior descending coronary ar-

tery, spontaneous resumption of ventricular activity occurred regularly after a period proportional to the amount of acetylcholine administered. It was thought that the risk of anoxic damage to the ischemic myocardium during arrest was small because of the concomitant pronounced decrease in oxygen requirement, and in this connection nothing more than transient T-wave alterations were seen electrocardiographically during these studies. ROGERS

Bell, A. L. L., Jr., Shimomura, S., Guthrie, W. J., Hempel, H. F., Fitzpatrick, H. F., and Begg, C. F.: Wedge Pulmonary Arteriography. Its Application in Congenital and Acquired Heart Disease. Radiology 73: 566 (Oct.), 1959.

During right heart catheterization a no.-7 Cournand catheter is manipulated into a pulmonary artery "wedge" position. After this position is confirmed by a pressure tracing, and while the patient holds his breath at full inspiration, 2 or 3 ml. of 70 per cent sodium 3-acetamide-2, 4, 6-triiodobenzoate are introduced through the catheter. During the injection an x-ray exposure is made. The catheter is immediately flushed with 5 to 10 ml. of physiologic saline and a repeat pressure tracing is obtained. This provides a wedge pulmonary arteriogram and provides an accurate reflection of the condition of the pulmonary vasculature. Untoward effects of the procedure consist of a transient paroxysm of coughing and a bitter taste. In 2 patients a pulmonary infarction-like process developed. These cleared in a few days, and both incidents occurred when the catheter was not flushed with normal saline following the picture. This method of examination should provide a safe clinical means for recognizing those patients in whom occlusive and presumably fixed changes in the pulmonary vascular resistance have occurred.

KITCHELL

Braunwald, E., Morrow, A. G., and Cooper, T.: Left Ventricular Angiocardiography in the Diagnosis of Persistent Atrioventricular Canal and Related Anomalies. Am. J. Cardiol. 4: 802 (Dec.), 1959.

Left ventricular angiocardiography has been accomplished by rapidly injecting 1 to 1.2 ml. per Kg. of concentrated radiopaque medium into the apex of the left ventricle through a no.-8 catheter inserted via a peripheral artery or, more often, through an opening in the atrial septum. Biplane roentgenograms exposed 4 to 6 per second thereafter allowed good visualization of this chamber and of adjacent areas receiving its outflow. Thus the presence of a shunt from the left ventricle to the right ventricle or atrium, or of regurgitation into the left atrium was documented. Clinical summaries and angiocardiograms were presented of 7 patients who had various types of septal defects, some with superimposed mitral valvular lesions. These cases illustrate the usefulness of this technic in the preoperative evaluation of patients with atypical findings suggesting atrioventricular cushion defects. ROGERS

Michelson, E., and Salik, J. O.: The Vascular Pattern of the Lung as Seen on Routine and Tomographic Studies. Radiology 73: 511 (Oct.), 1959.

The roentgen anatomy of the lung as seen on routine studies is a composite of contrasting shadows caused by air, blood, broncho-pulmonary tissues, and lymphatics. The interpretation of this pattern in health and disease is quite reliable. but there are limitations encountered depending on the site and type of the pathologic process. After some experience with tomographic localization of pulmonary structures, most of the vascular pattern can be identified on routine posteroanterior and lateral films. Examples of normal vascular architecture are noted and described by means of films, diagrams, and charts. By use of the basic vascular pattern in tomograms as a guide, most of the arteries and veins can be recognized on the conventional film.

KITCHELL

Stecken, A., and Weiss, U.: Tomography in Coarctation of the Aorta. Fortschr. Röntgenstr. 91: 151 (Aug.), 1959.

The results of tomography in 31 patients with coarctation of the aorta are summarized and illustrated. In the lateral or diagonal position, a typical, localized, short stenosis can be recognized from a notch in the dorsal contour of the aorta, the configuration of the stenotic region itself, ventral displacement of the filled esophagus, or calcification in the aortic wall. A long stenotic region can be recognized from a long distance between the origin of the subclavian artery and the post-stenotic aortic dilatation, or a low position of the subisthmic aortic impression in the esophagus or the aortic calcifications. A carefully executed tomogram, together with other clinical findings, frequently makes retrograde aortography superfluous. The method is also applicable in young persons. LEPESCHKIN

Zheutlin, N., Hughes, D., and O'Loughlin, B. J.: Radiographic Findings in Renal Vein Thrombosis. Radiology 73: 884 (Dec.), 1959.

After noting several instances of bizarre pyelographic patterns where occlusion of the renal

vein was the common denominator, the authors studied renal patterns in dogs with experimental renal vein occlusion. The clinical syndrome of renal vein thrombosis occurs most frequently (over 50 per cent) in children, with ileocolitis being the chief predisposing cause. In adults the condition may be secondary to thrombosis of the inferior vena cava with extension into the renal vein. Very seldom, according to the literature, has a definite diagnosis been made ante mortem in these cases. The authors present the findings in 3 patients with renal vein thrombosis and point out that the diagnosis may be suspected roentgenologically by the demonstration of an enlarged kidney, which on pyelography presents a "pseudocystic" appearance.

KITCHELL

SURGERY AND CARDIOVASCULAR DISEASE

Bailey, C. P., Musser, B. G., and Morse, D. P.: The Accomplishments of Open Heart Surgery. The Status of 35 Patients 18 to 36 Months Following the Operation. Am. J. Cardiol. 4: 147 (Aug.), 1959.

The courses of the authors' first 35 patients surviving 18 to 36 months after open-heart surgery (during 1956 and 1957) are summarized. A modified DeWall-type bubble oxygenator and 2 Sigmamotor pumps were used, maintaining an average circulation of over 3,000 ml. per minute. The patients' ages ranged from 29 to 58 years, and most had a cardiac functional classification of II or III. Twenty-three patients had acquired aortic stenosis, and all were greatly improved postoperatively. However, systolic aortic gradients of over 35 mm.Hg were found in 7 of the 10 patients studied after operation. A variety of operative complications were noted, most of which were resolved. Four patients had correction of a tetralogy of Fallot. There was a membranous ventricular septal defect in all, and each was closed by mattress sutures without causing an atrioventricular conduction disturbance. In the 2 patients catheterized postoperatively, the findings were normal. Repair of a ventricular septal defect alone was done in 3 patients, of congenital aortic stenosis in 3 patients, and of aortic insufficiency in 2 patients. The excellent improvement in 34 of the 35 patients spurred the authors on to develop even better technics and results.

ROGERS

Lillehei, C. W., Long, D. M., and Lepley, D., Jr.: Comparative Study of Polybrene and Protamine for Heparin-neutralization in Open-heart Surgery. Ann. Surg. 151: 11 (Jan.), 1960.

Heparinization is usually necessary with the use of extracorporeal circulation in open-heart surgery. Efficient drugs for heparin neutralization become of paramount importance in this situation. This study was carried out to compare the relative efficacy of polybrene and protamine sulfate in the neutralization of heparin. Two consecutive series of 50 patients each were compared. The quantity of postoperative drainage was used as the principal means for comparison. In animals there was no evidence of immediate or delayed toxicity to polybrene injected rapidly intravenously in amounts 4 to 8 times the amount of heparin given. In all the patients studied here, heparin was administered in a dosage of 1.5 mg. per Kg. of body weight for infants and children and 2.0 mg. per Kg. of body weight for adults. In those receiving protamine postoperatively the drug was given in a dosage of 2 mg. per mg. of heparin intravenously slowly in divided doses to prevent sequelae of hypotension. Polybrene was administered in a dosage range of 1 to 2 mg. of the drug per mg. of heparin given to the patient. The drug was diluted to contain 1 mg. per ml. of 5 per cent glucose in water and given intravenously slowly, over a 10-minute period. When patients with similar operative lesions were compared, it was noted that the postoperative drainage for the polybrene-treated patients averaged consistently less than that for the protamine-treated group. There was no instance of severe postoperative bleeding in the polybrene-treated group. In the protamine group 2 patients died within 24 hours after surgery contributed to by sustained bleeding effects. Careful analysis, however, indicated a wide overlap in the efficacy of the 2 agents, and meticulous hemostasis is still of great importance as well as attention to mechanical factors and careful crossmatching. It is also emphasized that when signs of excessive bleeding appear that the patient be returned to the operating room without delay for evacuation of clots and location of bleeding sources. The authors have noted that polybrene has been particularly effective in patients with extensive adhesions and in the deeply cyanotic group with abnormal clotting mechanisms.

LEVINSON

NEWS FROM
THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7-9170

OGLESBY PAUL, M.D.

Dr. Oglesby Paul, newly-elected President of the American Heart Association, has served as a Vice President of the Association from 1957-59 and as a member of its Board of Directors since 1956. He was Chairman of its Council on Community Service and Education from 1957-60. He has also been Secretary and First Vice President of the Chicago Heart Association, Chairman of its Council on Heart Services and Public Education, and a member of its Board.

Dr. Paul is Clinical Associate Professor of Medicine at the University of Illinois College of Medicine and Attending Physician at Chicago's Presbyterian-St. Luke's Hospital. He is also Consultant at the U.S. Naval Hospital in Great Lakes, Ill. and serves on the Board of the International Society of Cardiology Foundation.

Born in Villanova, Pa., Dr. Paul received his undergraduate degree *cum laude* from Harvard College in 1938 and his M.D., also *cum laude,* from Harvard Medical School in 1942. Later, as assistant to Dr. Paul D. White, he was in charge of a graduate course in cardiology sponsored by Harvard Medical School. He has served on the teaching staff at the University of Illinois Medical School where he twice received the Raymond Allen Instructorship Award from the junior class.

Dr. Paul is a member of the joint committee to study coronary heart and respiratory diseases under sponsorship of the National Heart Institute. He is a Fellow of the American Medical Association and of the American College of Physicians; a Diplomate of the National Board of Medical Examiners; and Chairman of the Television Committee of the American College of Physicians.

Association Names President-Elect; New Officers Chosen for 1960-61

J. Scott Butterworth, M.D., Associate Professor of Medicine, New York University Post-Graduate Medical School, was named President-Elect of the American Heart Association at its recent Annual Meeting in St. Louis. Oglesby Paul, M.D., Clinical Associate Professor of Medicine, University of Illinois College of Medicine, was installed as the Association's President for the 1960-61 term.

Retiring President A. Carlton Ernstene, M.D., Chairman, Division of Medicine, Cleveland Clinic, became Chairman of the Heart

Association's Central Committee for Medical and Community Program.

Newly-elected Vice Presidents of the Association were Brig. Gen. Philip P. Ardery, Louisville; Charles H. Rammelkamp, M.D., Cleveland; Helen B. Taussig, M.D., Baltimore; and James V. Warren, M.D., Galveston. Re-elected as Vice Presidents were John D. Brundage, Montclair, N.J.; Edgar Hull, M.D., New Orleans; Merritt H. Stiles, M.D., Spokane; and Ray B. Wiser, San Francisco.

1961 Subscription Renewals

Renewals of subscriptions for 1961 of *Circulation* and *Circulation Research*, official journals published by the Association, should be made through the Publishing Office, American Heart Association, 44 East 23rd Street, New York 10, N.Y. Annual Subscription rates are: *Circulation* (12 issues) $14 in the U.S. and Canada, $15 elsewhere. *Circulation Research* (6 issues) $9 in the U.S. and Canada, $10 elsewhere. (Special annual rate for full-time research fellows, $7.) Combined subscription to both journals, $21 in the U.S. and Canada, $23 elsewhere.

Meetings Calendar

January 9-12: White House Conference on Aging, Washington, D.C. Miss Esther C. Stamats, Department of Health, Education and Welfare, Washington 25, D.C.

February 8-11: American College of Radiology, Chicago. W. C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill.

March 13-16: National Health Council, New York. Philip E. Ryan, 1790 Broadway, New York 19, N.Y.

March 20-24: American Surgical Association, Boca Raton, Fla. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 10-14: American Physiological Society, Atlantic City. Ray G. Daggs, 9650 Wisconsin Ave., Washington 14, D.C.

April 17-20: American Academy of General Practice, Miami Beach. Mac F. Cahal, Volker at Brookside, Kansas City 12, Mo.

April 24-26: American Association for Thoracic Surgery, Philadelphia. Miss Ada Harvey, 7730 Carondelet Ave., St. Louis 5, Mo.

April 28-30: American Psychosomatic Society, Atlantic City. Morton F. Reiser, 265 Nassau Road, Roosevelt, N.Y.

April 30: American Federation for Clinical Research, Atlantic City. James E. Bryan, 250 W. 57th Street, New York 19, N.Y.

May 2-3: Association of American Physicians, Atlantic City. P. B. Beeson, Yale University School of Medicine, New Haven 11, Conn.

May 5-7: American Society of Internal Medicine, Miami Beach. G. T. Bates, 350 Post Street, San Francisco 8, Cal.

May 8-12: American College of Physicians, Miami Beach. E. C. Rosenow, Jr., 4200 Pine Street, Philadelphia 4, Pa.

May 16-20: American College of Cardiology, New York. Philip Reichert, 350 Fifth Avenue, New York 1, N.Y.

June 22-26: American College of Chest Physicians, New York. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

June 26-30: American Medical Association, New York. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Ill.

November 16-18: International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Mich.

Abroad

June 2-5: Latin-American Congress of Physical Medicine, Lisbon. C. L. deVictoria, 245 E. 17th Street, New York, N.Y.

August 22-25: International Pharmacological Meeting (First) Stockholm. A. Wretlind, Karolinska Institutet, Stockholm 60, Sweden.

September 3-10: Inter-American Congress of Radiology, Sao Paulo. W. Bomfin-Pontes, Rua Cesario Motta, No. 112, Sao Paulo, Brazil.

September 4-7: International Congress on Rheumatology, Rome. Prof. C. B. Ballabio, Clinica Medica Generale, Via F. Sforza 35, Milano, Italy.

September 6-12: International Congress of Human Genetics, Rome. Luigi Gedda, 5 Piazza Galeno, Rome, Italy.

September 10-15: International Neurological Congress, Rome. G. Alema, Viale Universita, 30 Rome, Italy.

September 18-22: International Congress of Neuroradiology, Rome. E. Valentino, Piazza Colonna 193, Rome, Italy.

1962

Fourth World Congress of Cardiology, Mexico City. I. Chavez, Ave. Cuauhtemoc, 300, Mexico, D.F.

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CIRCULATION

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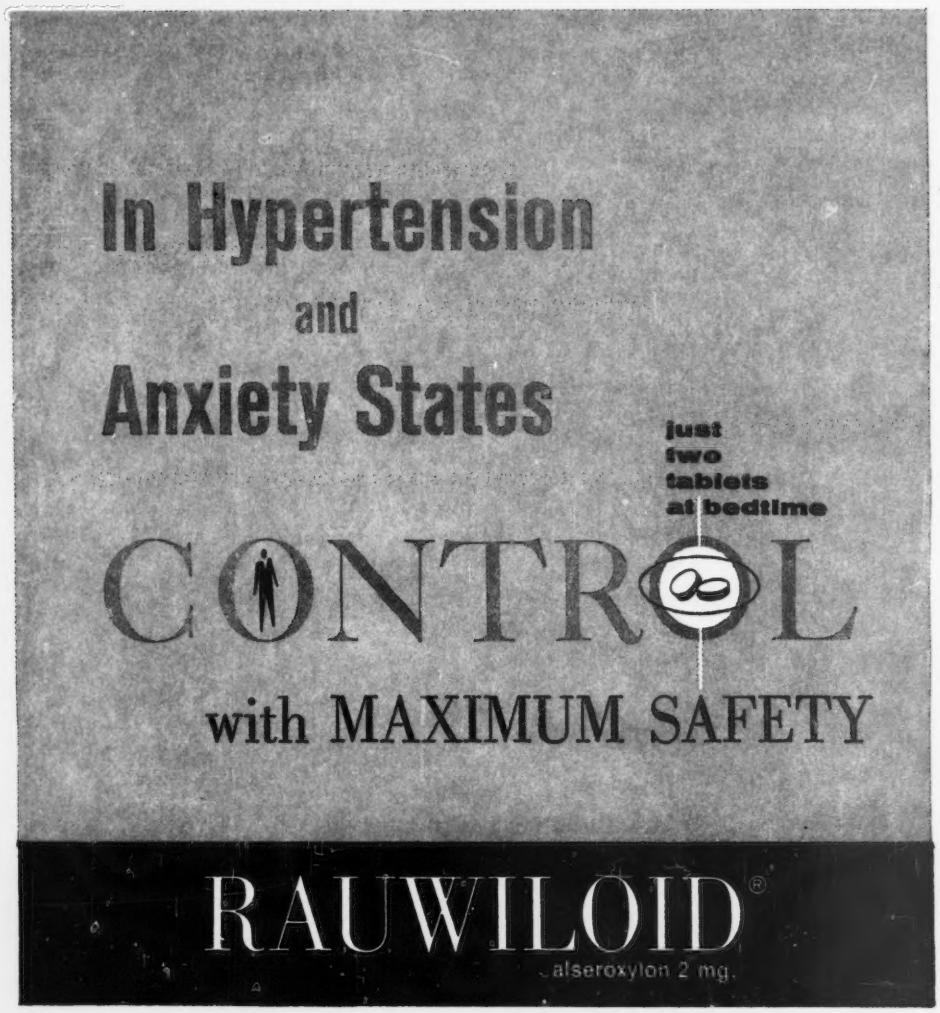

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Circulation

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